Doctoral Program in Clinical Research

Pediatric Graduate School and Pediatric Research Center

University of Helsinki, Finland

Outcomes of early childhood non-specific gastrointestinal symptoms – from diagnosis to long-term follow-up

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ACADEMIC DISSERTATION

To be publicly discussed, with the permission of the Faculty of Medicine of the University of Helsinki, in the Lecture Hall Hattivatti, Helsinki University Children's Hospital, on April 23rd, 2021, at 12 noon.

Helsinki 2021

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ISBN 978-951-51-7213-6 (nid.)

ISBN 978-951-51-7214-3 (PDF)

http:\\ethesis.helsinki.fi

Unigrafia Oy

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TIIVISTELMÄ

Tausta: Pienillä lapsilla esiintyy usein ruuansulatuskanavan oireita, kuten mahansisällön takaisinvirtausta ruokatorveen (refluksi) tai vatsakipua. Nämä ovat yleensä hyvänlaatuisia, toiminnallisia oireita. Pulauttelua tai oksentelua voidaan imeväisiässä epäillä myös oireeksi ruoka-allergiasta. Kehittyneissä maissa lasten yleisin sairaus ylemmässä ruoansulatuskanavassa on refluksitauti, jolla tarkoitetaan refluksin aiheuttamia hankalia oireita tai siihen liittyviä komplikaatioita kuten ruokatorvitulehdusta. Yläsuolikanavan tähystystutkimusta (gastroskopiaa) on perinteisesti käytetty ruokatorvitulehduksen todentamiseen tai poissulkemiseen potilailla, joilla on refluksitautiin viittaavia oireita, tai muiden tautien, kuten eosinofiilisen ruokatorvitulehduksen poissulkemiseksi.

Toiminnallisista oireista kärsivien erottaminen niistä, joiden oireet liittyvät sairauteen on usein haastavaa, vaikka ohjeita erilaisten yläsuolikanavan oireiden erotusdiagnostiikkaa helpottamaan on saatavana. Tähystystutkimuksen hyvä saatavuus ja puuttuva tieto yleisesti esiintyvien yläsuolikanavan oireiden pitkäaikaisennusteesta ovat mahdollisesti lisänneet pienille lapsille suoritettujen yläsuolikanavan tähystystutkimusten määrää. Kliininen kokemus ei kuitenkaan ole tukenut ajatusta tähystystutkimuksen diagnostisesta hyödystä pienillä lapsilla. Lisäksi tietoa oireiden pitkäaikaisennusteesta on vähän.

Tavoite: Tämän tutkimuksen tarkoituksena oli tutkia yläsuolikanavan tähystystutkimuksen diagnostista merkitystä alle seitsemän vuoden ikäisillä lapsilla, joilla esiintyy pidempiaikaisia, epäspesifisiä maha-suolikanavan oireita. Haluttiin myös lisätä tietoa siitä, miten varhaislapsuudessa refluksisairauteen tai suolioireiseen lehmänmaitoallergiaan viitanneet oireet näkyivät lasten elämässä kouluiässä.

Potilaat ja menetelmät: Ensimmäisessä osatyössä tutkimuspopulaation muodostivat alle 7-vuoden ikäiset lapset, joille oli tehty vuosien 2006-2016 aikana Helsingin yliopistollisen sairaalan Lastenklinikalla ensimmäinen yläsuolikanavan tähystystutkimus pidempiaikaisten, epäspesifisten oireiden vuoksi (n=1850). Poissulkukriteereinä olivat akuutit oireet, tiedossa oleva sairaus, jonka vuoksi tähystys tehtiin tai toimenpidetarve, sekä pään, kaulan ja hengitysteiden tai mahasuolikanavan synnynnäiset epämuodostumat. Myös potilaat, joilla tähystys liittyi koepalojen ottoon positiivisten vasta-aineiden perusteella epäillyssä keliakiassa, poissuljettiin tutkimuksesta. Jäljelle jääneiden lasten (n=666) potilaskertomuksista haettiin takautuvasti tiedot tähystykseen johtaneista oireista, happosalpaajalääkityksen käytöstä ja tähystystutkimuksen tuloksista ja tulosten vaikutuksesta jatkohoitosuunnitelmaan. Toisessa osatyössä tarkasteltiin lapsia, joille yläsuolikanavan tähystystutkimus oli tehty refluksisairauden epäilyn vuoksi (n=254). Tähystystutkimuksen aikaisia tuloksia tarkasteltiin sen valossa, oliko lapsella refluksille altistavaa perussairautta. Tuloksia tarkasteltiin vielä erikseen niiden lasten osalta, joilla refluksin vuoksi varhaislapsuudessa tehty tähystystutkimus oli ollut löydöksiltään normaali (n=199). Kanta-potilasrekisteristä ja reseptitietokannasta haettiin tietoa lasten ajankohtaiseen refluksiin liitetyistä oireista ja kahden edeltävän vuoden happosalpaajalääkkeiden käytöstä. Tästä joukosta ne potilaat, joiden äidinkieli on suomi (n=175), kutsuttiin sähköiseen kyselytutkimukseen koskien ajankohtaisia oireita, lääkityksiä ja elämänlaatua.

Kolmannessa osatyössä tutkittiin lapsia, jotka olivat osallistuneet aikaisempaan tutkimusprojektiin suolioireisen lehmänmaitoallergian epäilyn vuoksi ja joille oli tehty varhaislapsuudessa kaksoissokkoutettu ruoka-altistus (n=57). Suurimmalla osalla (68 %) altistus ei ollut vahvistanut ruoka-aineallergia epäilyä. Näiden lasten äidit kutsuttiin vastaamaan sähköiseen kyselytutkimukseen lasten nykyisistä vatsaoireista, ruokavaliosta ja elämänlaadusta.

Tulokset: Suurimmalla osalla (81%) ensimmäisen osatyön 666 lapsesta tähystyksen tulokset olivat täysin normaalit. Erityisesti imeväisillä tähystyslöydökset olivat vähäisiä. Yleisimmät tähystykseen johtavat oireet liittyivät mahansisällön takaisinvirtaukseen, ja yleisin syy tähystykselle oli ollut refluksitaudin epäily. Yhdelläkään lapsella ei todettu haavaista (erosiivista) ruokatorvitulehdusta. Yleisin histologinen löydös oli lievä tai kohtalainen ruokatorvitulehdus (9%). Histologisten löydösten määrä lisääntyi merkitsevästi iän myötä. Happolääkityksen mahdollinen käyttö tähystyksen aikaan ei vaikuttanut merkitsevästi histologisten löydösten määrään. Yllättäen löytyneitä keliakiatapauksia ei ollut, ja histologisesti vahvistettujen eosinofiilisten ruokatorvitulehdusten lukumäärä tässä joukossa oli erittäin pieni (0.3%). Lapsilla, joilla diagnosoitiin tulehduksellinen suolistosairaus samanaikaisella paksusuolentähystyksellä, yläsuolikanavan tähystyslöydökset (useimmiten lievä gastriitti) eivät vaatineet hoitoa. Riippumatta yläsuolikanavan tähystyksen alkuperäisestä syystä, tähystystutkimuksen tulokset vaikuttivat jatkohoitoon alle 10%:lla lapsista.

Lapsilla, joilla oli epäilty refluksitautia, tähystystutkimus oli täysin normaali 83%:lla. Oksentelu oli yleisin refluksitaudin epäilyyn liitetty oire, mutta mikään tähystykseen johtaneista oireista ei ennakoinut positiivisia tähystyslöydöksiä. Osalle potilaista (39%) oli tehty myös ruokatorven pH-mittaus, mutta poikkeavan runsas hapan takaisinvirtaus ruokatorvessa ei ennustanut positiivisia tähystyslöydöksiä. Uusintatähystys oli tehty ainakin kertaalleen 31 potilaalle ja näissä tähystyksissä ruokatorven limakalvon muutosten histologinen aste pysyi ennallaan tai muuttui lievemmäksi. Sairauskertomustietojen perusteella refluksioireiden esiintyvyys oli yleisesti terveillä lapsilla keskimäärin kahdeksan vuotta diagnostisen tähystystutkimuksen jälkeen vähäinen. Pitkäaikainen happosalpaajalääkitys oli käytössä 4%:lla aiemmin takaisinvirtauksen vuoksi normaalein tuloksin tähystetyistä lapsista, ja suurimmalla osalla näistä lapsista oli jokin takaisinvirtaukselle altistava perussairaus. Kyselytutkimukseen kutsutuista 175 suomenkielisistä perheistä 51 (29%) palautti kyselylomakkeen, jossa kysyttiin lapsen ajankohtaisista, vanhempien refluksiin liittämistä oireista ja happosalpaajalääkkeiden käytöstä. Vastauksissan 24% vanhemmista ilmoitti lapsensa kärsineen päivittäin tai viikottain jostakin refluksiin liitetystä oireesta edeltävien 3 kk aikana. Happosalpaajalääkkeiden käyttöä raportoitiin vähän, mutta moni vanhempi kertoi lapsensa noudattavan jotain erityisruokavaliota. Lasten vatsaoireisiin liittyvä elämänlaatu oli hyvä sekä vanhempien, että tutkimuskyselyyn vastanneiden yli 8-vuotiaiden lasten raportoimana.

Niistä lapsista, joilla oli aikaisemmin epäilty suolisto-oireiden pohjalta lehmänmaitoallergiaa, kaikilla oli keskimäärin viiden seurantavuoden jälkeen normaali ruokavalio, ja äidit raportoivat lastensa elämänlaadun

hyväksi. Kahdelle altistusnegatiiviselle lapselle, joiden vatsaoireet olivat jatkuneet, oli tehty ruoka-altistuksen jälkeen yläsuolikanavan tähystystutkimus normaalein tuloksin.

Johtopäätökset: Pienillä lapsilla, joilla esiintyy pidempiaikaisia, epäspesifisiä maha-suolikanavan oireita, yläsuolikanavan tähystystutkimuksen diagnostinen rooli on tämän työn perusteella vähäinen. Positiivisia tähystyslöydöksiä oli vähän ja niistä suurin osa oli luonteeltaan epäspesifejä eivätkä löydökset johtaneet muutoksiin lapsen jatkohoidossa tai –seurannassa. Lapsilla, joille oli tehty useampi tähystystutkimus, histologiset muutokset joko pysyivät ennallaan tai lievenivät. Varhaislapsuuden oireperusteisten sairauksien epäilyyn ei liittynyt pitkäaikaissairastavuutta kouluiässä. Refluksitaudin epäilyyn ei liittynyt myöskään pitkäkestoista happosalpaajalääkkeen käyttöä, varsinkaan jos lapsella ei ollut refluksille altistavia perussairauksia. Aiempaan suolioireiseen maitoallergiaan tai sen epäilyyn ei liittynyt myöhempiä ruokavaliorajoituksia. Pieniä lapsia tähystystoimenpiteeseen lähettävien lääkärien olisi tärkeä olla tietoisia yläsuolikanavan tähystystutkimusten vähäisistä löydöksistä erilaisten epäspesifisten vatsaoireiden selvittelyssä. Myös toimenpidettä suorittavassa yksikössä tarvitaan selkeät, tieteelliseen näyttöön perustuvat toimenpideindikaatiot, jotta tähystystoimenpiteet kohdistuvat niistä eniten hyötyville.

ABSTRACT

Background: Small children often experience gastrointestinal (GI) symptoms such as regurgitation or abdominal pain. These are usually benign, functional symptoms. In infants, spilling or vomiting can also be suspected to be a symptom of food allergy. In children of developed countries, the most common organic disease in the upper GI tract is gastroesophageal reflux disease (GERD), which refers to troublesome symptoms caused by reflux and related complications such as esophagitis. Upper endoscopy has traditionally been used to verify or exclude esophagitis in patients with symptoms suggestive of GERD, or to exclude other diseases such as eosinophilic esophagitis.

Distinguishing children with functional symptoms from those in whom symptoms are associated with disease is often challenging, although guidelines to facilitate differential diagnosis are available. Good availability of endoscopy and lack of data on the long-term prognosis of common upper GI symptoms may have increased the number of upper endoscopies in young children. However, clinical experience suggests that upper endoscopies performed on young patients with non-acute, non-specific symptoms seldom provide clinically relevant data.

Aim: This study aimed to evaluate the diagnostic role of upper endoscopy in children younger than 7 years presenting with non-acute, non-specific GI symptoms. The aim was also to estimate school-age outcomes of symptoms suggestive of GERD or cow's milk protein allergy with GI symptoms (GI-CMPA) in early childhood.

Patients and methods: The first substudy included children who had undergone primary upper endoscopy at Helsinki University Children's Hospital in 2006-2016. At an age younger than 7 years, these children had presented with non-specific, non-acute symptoms (n=1850). Patients with acute symptoms, a known disease, or a foreign body for which endoscopy was performed, and congenital malformations of the head, neck and respiratory tract or GI tract, as well as patients with antibody-positive suspected celiac disease were excluded from the study. The remaining patients' records (n=666) were retrospectively searched for data on the symptoms leading to upper endoscopy, the use of anti-acid medication at the time of endoscopy, the endoscopy results, and the impact of the results on the follow-up or treatment plans.
In the second substudy, children who had undergone primary upper endoscopy due to suspicion of GERD (n=254) were further investigated by evaluating the effect of predisposing conditions to GER on endoscopy findings. Also, the current well-being and anti-acid medication use of children in whom the primary upper endoscopy had resulted in normal findings (n=199) was assessed using the Patient Data Repository and Prescription Service. Of these patients, those whose native language is Finnish (n=175) were invited to an electronic follow-up survey on current symptoms, medications, and GI health-related quality of life (QoL).

The third substudy investigated children who had in early childhood undergone a double-blind, placebo-controlled food challenge due to suspicion of GI-CMPA (n=57). The suspicion of GI-CMPA had not been confirmed in the majority (68%) of these patients. Mothers of both challenge-positive and challenge-negative children were invited to respond to an electronic follow-up questionnaire on children's current GI symptoms, diet, and QoL.

Results: In the majority (81%) of the 666 children who had undergone primary upper endoscopy to investigate non-acute, non-specific symptoms, the endoscopy results were completely normal. Especially in infants, the findings were minor. The most common symptoms leading to endoscopy were related to gastroesophageal reflux, and the most common cause of endoscopy was suspicion of GERD. None in the cohort had erosive esophagitis. The most common histological finding was mild to moderate histological esophagitis (9%). The number of histological findings increased significantly with age. The use of acid blocker medication at the time of endoscopy did not significantly affect the histological findings. There were no unsuspected celiac disease cases, and the number of histologically confirmed eosinophilic esophagitis in this group was low (0.3%). In children diagnosed with inflammatory bowel disease using concomitant colonoscopy, upper endoscopy findings (most often mild gastritis) did not require active treatment. Regardless of the original cause of the primary upper endoscopy, the results affected treatment or follow-up plans in less than 10% of the patients.

In children with suspicion of GERD, the upper endoscopy findings were normal in 83%. Vomiting was the most common symptom associated with suspicion of GERD, but none of the symptoms leading to the endoscopy predicted positive findings. Some of the children (39%) had also undergone 24-hour pH-monitoring, but increased esophageal acid reflux did not predict positive endoscopy findings. Thirty-one patients had undergone more than one upper endoscopy. In these patients, the histological degree of changes in the esophageal biopsies remained unchanged or became less severe. Based on medical records, after a median of eight years of follow-up, the otherwise healthy children had seldom reported reflux-related complaints. However, 4% of children with initially normal primary upper endoscopy findings were currently using long-term acid blocker medication, with most of them having underlying conditions predisposing them to GER. Of the 175 Finnish-speaking families who were invited to the follow-up survey, 51 parents (29%) completed the questionnaire on their child’s current reflux symptoms and use of anti-acid medications. Current daily or weekly occurring reflux-related complaints were parentally reported by 24% of survey responders. The use of anti-acid medications was uncommon, but many parents described their child to use a restricted diet. The GI health-related QoL was reported as good by both parents and children older than 8 years of age who responded to the survey.
Of the children who had previously undergone a double-blind, placebo-controlled food challenge for symptoms suggestive of GI-CMPA, all had a normal diet after an average of five follow-up years, and

mothers reported their children's quality of life as good. After the food challenge, two challenge-negative children with on-going GI symptoms had also undergone an upper endoscopy with normal results.

Conclusions: Based on this study, the diagnostic role of upper endoscopy is minimal in young children presenting with non-specific, non-acute symptoms. There were only a few positive findings in the endoscopy, most non-specific, and the findings rarely led to changes in the child's treatment or follow-up plan. In children who had undergone more than one upper endoscopy, the histological changes either remained unchanged or became less severe. The suspicion of symptom-based diseases in early childhood was not associated with long-term morbidity at school age. Also, the early childhood symptoms leading to suspicion of GERD were not associated with long-term use of acid blocker medications at school age, especially if the child did not have underlying diseases predisposing to GERD. Moreover, no subsequent dietary restrictions occurred in children investigated due to an early childhood suspicion of GI-CMPA.
It is essential to educate clinicians referring children to upper endoscopy about the rarity of diagnostic findings in association with non-acute, non-specific GI symptoms in young children. Also, centers performing pediatric upper endoscopies should ensure that their endoscopy indications are in line with the scientifically approved data, reserving the endoscopy for those who most benefit from it.

ABBREVIATIONS

CI Confidence interval

CM Cow's milk

CMPA Cow's milk protein allergy

CNS Central nervous system

DBPCFC Double-blind, placebo-controlled food challenge

EGD Esophagogastroduodenoscopy

ENS Enteric nervous system

EoE Eosinophilic esophagitis

EPX eosinophil peroxidase

ESPGHAN European Society of Pediatric Gastroenterology, Hepatology and Nutrition

FD Functional dyspepsia

FGID Functional gastrointestinal disease

FPIES Food protein-induced enterocolitis syndrome

GER Gastroesophageal reflux

GERD Gastroesophageal reflux disease

GI Gastrointestinal

GI-CMPA Gastrointestinally manifesting cow's milk protein allergy

HPF High-power field

HRQoL Health-related quality of life

IBD Inflammatory bowel disease

LES Lower esophageal sphincter

MII-pH Combined multichannel intraluminal impedance and 24-hour pH-monitoring

NERD Non-erosive reflux disease

PedsQL Pediatric quality of life questionnaire

PPI Proton pump inhibitor

PSI Parenting Stress Index -questionnaire

QoL Quality of life

RAP Recurrent abdominal pain

TRLES Transient relaxation of the lower esophageal sphincter

List of original publications

I Helin N, Kolho K-L, Rintala R, Merras-Salmio L. Upper endoscopy for non-acute non-specific symptoms is seldom beneficial for children under the age of seven. Acta Paediatrica. 2020 Apr;109(4):827-835.

II Helin N, Kolho K-L, Merras-Salmio L: Parentally reported early childhood upper gastrointestinal symptoms alleviate at school-age. Submitted

III Helin N, Kolho K-L, Qvist E, Mäkelä M, Merras-Salmio L. Gastrointestinal Symptoms of Food Challenge-proven Non-IgE Cow's Milk Allergy Are Dissipated by Early School Age. Journal of Pediatric Gastroenterology and Nutrition. 2018 Apr;66(4):598-602.

The publications are referred to in the text by their Roman numerals.

1 Introduction

Various gastrointestinal (GI) symptoms are common throughout childhood, [1–3] and patients presenting such symptoms as heartburn, regurgitation, vomiting, or recurrent abdominal pain are frequently seen at the general pediatrician's office.[4,5] Although benign, these symptoms impose burden onto patients and their families and on the health-care system due to increased numbers of appointments, medications, and investigations.[6–9] Most of these non-specific GI symptoms are classified as functional gastrointestinal disorders (FGIDs), also known as disorders of the gut-brain axis.[10] Symptoms may arise from all parts of the digestive tract and can be recurrent or continuous. Functional GI symptoms have been associated with significantly reduced quality of life.[11,12]

The prevalence of individual FGID symptoms varies with age,[1,13] and over one-third of infants, 20% of toddlers, and 25% of children older than four years present with at least one FGID.[14] Infant regurgitation is the most common FGID in infancy [14,15] but by age 4-6 years different abdominal pain-related disorders dominate.[1] In older children, recurrent abdominal pain is common, and its prevalence increases steadily with age [16]. The Rome IV clinical guidelines govern the diagnosis of FGIDs.[1,13,17–19] Other guidelines are also available.[20]

The common disease related to upper GI symptoms is gastroesophageal reflux disease (GERD).[15] It is defined as GER that causes troublesome symptoms and complications, such as esophagitis, and affects daily functioning.[21] GERD has often been diagnosed without invasive methods using history and clinical examination, but if complications, such as esophagitis, are suspected the diagnosis is based on biopsies obtained during the upper endoscopy (esophagogastroduodenoscopy, EGD). Esophagitis can present with solely histological changes with normal macroscopic evaluation or as erosive when abnormal changes in the esophageal mucosa are visible during the EGD. The incidence of erosive esophagitis is known to increase with age, but data are limited in infants and young children.[22]

However, as symptoms do not predict the endoscopy outcome, clinical decision-making is challenging.[23] Also, histological changes related to GER are not disease-specific and some inflammatory cells have been found in non-symptomatic patients as well.[24] There are several sub-groups of patients for which EGD is an important tool in diagnosis and treatment, and patients belonging to these subgroups are not included in this study. Patient groups in which EGDs are indicated according to the guidelines include:

- patients with acute hematemesis with or without pre-diagnosed portal hypertension
- suspicion of a foreign body or caustic injury
- congenital malformations of the upper respiratory, the head and neck, or the GI tract
- graft versus host disease

EGD is also used to place gastrostomy, obtain biopsies to culture *Helicobacter pylori*, and diagnose antibody-positive pediatric celiac disease. Patients with these indications for EGD are excluded from this study. Although EGD in children is considered safe, the pediatric EGDs are performed under general

anesthesia, which adds to the endoscopy's potential adverse effects. This study focuses only on the symptoms and findings from the upper GI tract.

A distinct group of childhood diseases diagnosed using endoscopy is the inflammatory bowel diseases (IBDs). IBDs are classified into Crohn's disease, unclassified IBD, and ulcerative colitis, and their incidence has been rising for the last few decades.[25–27] Often, IBD diagnosed at a young age has severe symptoms and an aggressive disease course. Patients often present with bloody diarrhea and abdominal pain, and the diagnosis is based on colonoscopy findings, but all children also undergo a concomitant EGD as a part of the recommended workup.[28] In addition to symptom severity, measuring fecal calprotectin has helped distinguish patients with suspected colitis from patients with non-IBD rectal bleeding.[29] The diagnosis and classification of IBD are determined by biopsies obtained from both the upper and lower GI tract. Also, magnetic resonance enterography and imaging studies may be used.

Different from GERD-related esophagitis is eosinophilic esophagitis (EoE), an entity characterized by an increased number (>15/high-power field, HPF) of eosinophils in the histological examination of esophageal biopsies.[30,31] EoE is an allergy-related disease with a variable clinical picture. In adults, EoE is strongly associated with swallowing problems, but in children it may also present with various non-specific symptoms.[32] The prevalence of EoE has increased in recent decades [33,34], but knowledge of the disease has improved markedly during the last five years.[32]

Food allergy with GI symptoms may present with non-specific upper GI symptoms such as vomiting or abdominal pain. In immunoglobulin E (IgE) -mediated allergies, vomiting may be a sign of anaphylaxis but is typically accompanied by other symptoms of generalized allergic reactions such as breathing problems and skin flushing. If food allergy presents with GI symptoms only, it is usually mediated by another pathway and is called a non-IgE allergy.[35] The most common non-IgE food allergy is cow's milk protein allergy (CMPA), which predominantly presents with abdominal symptoms and develops several hours after ingestion. A double-blind, placebo-controlled food challenge (DBPCFC) is considered the gold standard of diagnosis.[36,37] Most cases with suspicion of CMPA causing GI symptoms (GI-CMPA) are not confirmed in the DBPCFC,[37] and the only symptom significantly associated with DBPCFC-confirmed non-IgE CMPA has been loose stool.[38]

The good availability of endoscopy has led to a rising number of children undergoing EGD for non-specific symptoms.[39] However, clinical experience and previous research [40–42] suggest that EGD seldom provides clinically significant findings, especially in the youngest children. If guideline recommendations for the EGD indications are followed, the diagnostic yield has been reported to be as high as 76%.[43]

This study aimed to investigate the role of EGD in the diagnostic process of children younger than seven years presenting with non-specific, non-acute upper GI symptoms and to gain new data on long-term outcomes of the two commonly suspected conditions of GERD and GI-CMPA.

2 Review of the literature

2.1 Pediatric disorders of the upper gastrointestinal tract

2.1.1 Introduction

The functions of the GI tract are essential in preserving life. The GI tract starts at the mouth, where salivary glands secrete enzymes to initiate carbohydrate digestion. The downward peristalsis of the esophagus passes the food to the stomach, which, together with the small bowel, oversees the digestion and absorption via both mechanical and chemical mechanisms. The waste is expelled via the large bowel and anus, and the complex network needs all parts to function well in order to maintain stability.[44] Many of the symptoms and complaints arising from the GI tract are defined and diagnosed using symptom-based, patient-centered clinical criteria.

2.1.2 Functional gastrointestinal disorders (FGIDs)

Background and prevalence

Functional gastrointestinal disorders (FGIDs) include various chronic or recurrent symptoms of GI origin that are not explained by structural or biochemical abnormalities or that, after appropriate medical evaluation, cannot be attributed to another medical condition.[1,10,13,19] They are currently best understood as bio-psychosocial disorders without specific organic etiology [45] with an association with alterations in the interaction between the gut and the brain.[46,47] FGIDs are common in children and adolescents and may lead to repeated contacts with the health care system and impaired quality of life.[9,48,49] The FGID diagnosis in children follows the Rome criteria, which are based on the child's symptoms and are always, to some extent, subjective. The Rome criteria were developed in a working committee by reviewing the literature and a consensus process and first published for adult patients in 1994. Since 1999, the criteria have also been established for children. The most recent (fourth revision) Rome criteria were published in 2016. According to the criteria, childhood FGIDs fall into three primary categories: functional nausea and vomiting disorders, functional abdominal pain disorders, and functional defecation disorders, but only disorders affecting the upper GI tract are considered in this study. The pediatric Rome IV criteria have been established for infants and toddlers (0-3 years) [13] and older children (4-18 years).[1]

The prevalence of individual FGIDs varies with age. FGIDs are estimated to affect 25% of children from infancy through teenage years.[2,14,50] In a systematic review, Ferreira-Maia *et al.* estimated pediatric FGID prevalence rates of 27.1-38.0%.[51] However, the epidemiology of FGIDs is challenging due to heterogeneity of the available studies.[52] In infants and toddlers, additional challenges in diagnosis lie in

their inability to communicate and distinguish emotional and physical distress and uncovering how parents perceive and react to their child's symptoms.[13,19]

Role of gut microbiota

The gut microbiota refers to the population of micro-organisms present in the gut.[53] The human gut microbiota includes bacteria, archaea, yeasts, and viruses.[54–56] The gut microbiome refers to the genome of all gut microbes.[57,58] The bacteria are not spread uniformly throughout the GI tract, but different parts have their own distinct composition of bacterial inhabitants.[59] The relationship between the host and the microbiota can be commensal, symbiotic, or pathogenic. In the best scenario, both benefit from one another.

The child gut microbiota differs from the adult microbiota. The transition towards adult-type gut microbiota is slow and takes place during early childhood.[60–62] In infancy and childhood, the gut microbiota is more readily shaped by nutrition and environmental agents than during adulthood.[63] It has been estimated that an adult-type composition of gut microbiome is established during the first few years of life.[64,65] This time is crucial for the later homeostasis, and if this process is disturbed by infections, medications such as antibiotics or acid blockers, or unfavorable dietary habits, this may lead to dysbiosis by reducing microbiota stability and diversity.[66–69] This, in turn, may lead to disturbed function of the GI tract. Dysregulation of the early gut microbiota has also been associated with other long-term consequences such as asthma,[70] atopic eczema,[71] allergic rhinitis,[72] obesity,[73] and neuropsychiatric disorders.[74] Evidence suggests that the intestinal microbiota plays a key role in FGIDs, but there is no clear consensus regarding the actual microbes associated with individual FGIDs.[75–77]

Role of immune response

The microbiota is in close contact with the immune system. Early exposure to variable environmental microbes is obligatory for developing a healthy immune system, which in turn guides microbiota to homeostasis and promotes health.[65,78–80] It has been proposed that bacteria producing short-chain fatty acid butyrate can positively modulate immune tolerance.[81–83]

Microbiota-gut-brain axis

The microbiota-gut-brain axis transmits bidirectional communication between the gut and the central nervous system and links the brain's emotional and cognitive centers with peripheral gut functions.[84] It is a network of the gut microbiota, autonomic nervous system, enteric nervous system (ENS), and the central nervous system's (CNS's) neuroendocrine and neuroimmune compounds.[85,86] The ENS directly and autonomically controls the GI tract [87] and coordinates the gut motility and controls fluid movement. Anatomically ENS can be crudely subdivided into the submucosal plexus and the myenteric plexus.[88] The

information from the ENS to the CNS is shared using the vagus nerve's afferent sensory pathways and via the sympathetic nervous system through efferent motor pathways of the prevertebral ganglia.[89] Also, the gut microbiota has been reported to utilizise the vagus nerve to communicate directly with both the CNS and ENS.[90,91] However, the precise mechanisms of the bi-directional communication in the microbiota-gut-brain axis are not yet completely understood.[92]

Stress and FGIDs

Psychological stress is considered to have an important role in the pathophysiology of FGIDs.[1,93] The impact of stress on FGID development is, however, only partially understood by studying exposure because the impact of stress is, in large part, determined by an individual's appraisal and response to a given stressor.[94,95] Individual coping methods have been associated with symptom severity, functional disability, and anxiety or depression in children with functional abdominal pain.[96–98] Genetics, environmental factors, and sociocultural influences may affect one's susceptibility to stress, psychological state, and coping skills. These factors are also known to influence the risk for gut dysfunction.[10] Psychological and physical stressors activate the hypothalamic-pituitary-adrenal axis, resulting in the release of corticotropin-releasing factor, adrenocorticotrophic hormone, glucocorticoids, and catecholamines (norepinephrine and epinephrine) into the circulatory system. They also activate the autonomic nervous system and evoke the neuronal release of norepinephrine and other neurotransmitter substances in peripheral tissues.[99] The activation of this cascade results in motility changes in the gut.[100]

Role of family history in FGIDs

Strong evidence from twin studies indicates that the tendency for FGIDs is genetic.[101,102] Some studies with data on children are also available. Levy *et al.* found that both GI- and non-GI symptoms were more common in children whose mothers had FGID.[103] Also, it appeared that a solicitous parental response to the child’s complaints led to more disability. Similarly, Lewis *et al.* conducted a childhood FGID prevalence study and reported that children were significantly more likely to qualify for an FGID if their mother also qualified for an FGID.[2] Some studies on FGID genetics are available, but the findings are preliminary.[104–106]

Parental depression, anxiety, and somatization are also associated with a higher rate of abdominal complaints in offspring.[46,107] The concept of illness behavior and the parent’s reaction to a child’s complaints have an impact. Parental responses such as discouraging activity, expressing concern, and providing comfort may serve to reinforce and maintain illness behaviors inadvertently.[108]

Other conditions associated with FGIDs

CMPA has been proposed as a predisposing or comorbid disease in patients with long-term FGIDs.[109,110]

Obesity has been associated with disturbances in the gut-brain axis. Tambucci *et al.* reported that almost half (47.6%) of obese or overweight children had an FGID, compared with 17.3% of normal-weight children.[111] Phatak *et al.* and Ho *et al.* have reported similar results.[112–114]

Colman *et al.* conducted a prospective study on FGIDs in children with persistent asthma and 16.4% of them met the criteria for an FGID.[115]

Autism spectrum disorder is a heterogeneous neurodevelopmental disorder with impairment in many of the features involved in communication, and patients are reported frequently to suffer from various FGIDs.[116]

FGIDs and the quality of life

FGIDs have been shown to reduce the quality of life in both children and their parents. A study by Lewis *et al.* discovered that children with FGID have significantly lower quality of life scores than same-aged children without FGIDs.[2] Van Tilburg *et al.* used a similar cohort of 0-3-year-olds to study the parental quality of life related to their child's health issues and found that parents of infants whose symptoms qualified to an FGID reported significantly lower quality of life than parents of infants without FGID.[117] Also, Vandenplas *et al.* state in a recent review article that FGIDs during infancy, although mostly benign and self-limited, cause a significant reduction in parents' quality of life.[118]

2.1.3 FGIDs in infants and toddlers

Prevalence

Estimated prevalence of the most FGIDs in infants and toddlers is shown in Table 1.

Table 1

Prevalence of functional gastrointestinal disorders in neonates and toddlers according to the Rome IV criteria.

Disorder	**Typical age**	**Prevalence %**
Infant regurgitation (GER)	3 weeks-12 months	41-67
Infant rumination syndrome	3-8 months	2
Infant colic	0-5 months	5-19
Cyclic vomiting syndrome	Wide range	3

modified from Benninga et al.[13]

Infant regurgitation (gastroesophageal reflux, GER)

The most common FGID in infancy is infant regurgitation which is reported to occur in two-thirds of infants at the age of 4 months.[15,51,117] The Rome IV diagnostic criteria for infant regurgitation include regurgitation in an otherwise healthy infant aged three weeks to 12 months at least two times per day over at least three weeks and with no alarming signs of any illness such as hematemesis, retching, aspiration, and apnea or feeding/swallowing difficulties, or abnormal posturing.[13] Martin *et al.* showed in their prospective study that spilling of most feeds each day was typical in infancy and reached a peak prevalence of 41-87% at age 3-4 months thereafter declining to < 5% at age 13-14 months.[119] Campanozzi *et al.* reported similar findings.[120] Different diagnostic criteria may explain the wide range in prevalence of regurgitation in the past.

GER is defined as the involuntary retrograde passage of gastric contents into the esophagus with or without visible regurgitation.[21,121] During infancy, the lower part of the esophagus, including the esophagogastric junction, is located inside the thoracic cavity, and as the child grows the junction descends into the abdominal cavity. The physiological cause of GER is the brief, transient relaxation period of the lower esophageal sphincter (LES). These brief relaxations are independent of swallowing.[122,123] In children without neurological disabilities, transient relaxations of the LES (TRLES) are the most common cause for GER, but the LES resting tone is typically normal. Only the duration and number of the TRLES are increased.[124,125] Also, infants are prone to GER because of their large fluid intake and the supine body position leading to constant immersion of the gastroesophageal junction.[126]

In infants, the prognosis of GER is excellent, symptoms resolve without treatment in nearly all patients after the first year of life.[127,128] However, long-term follow-up of children presenting with troublesome GER symptoms in infancy is lacking. Funderburk *et al.* studied pre- and full-term infants presenting with persistent vomiting, irritability, arching, apnea, cough, wheezing, and feeding difficulties, among other reflux-related symptoms, and using combined multichannel intraluminal impedance (MII) and 24-hour pH monitoring (MII-pH) found that most of the suspected reflux-related behavior did not correlate with reflux events in the recording.[129]

There are known risk groups for GER. Prematurity,[130] neurological impairment including mental retardation, epilepsy,[124,131] and obesity,[132] are often mentioned. However, children with psychomotor retardation are especially prone to GER and an incidence of 80% and over has been reported.[133] The pathophysiological mechanism for GER in neurologically impaired children has been proposed to be the absent tone of the LES. Also, poor motility of the whole GI tract may result in delayed gastric emptying and further promote GER.[125,134] Other diseases associated with clinically significant GER are muscle disorders [135] and chronic lung diseases such as cystic fibrosis.[136]

The association between CMPA and GER remains unproven.[38,137] In a recent review by Pensabene *et al.*,the authors state that persistent regurgitation might be a non-specific symptom of CMPA in young

infants.[110] Salvatore *et al.* discussed in their study that irritability, crying, pain, sleep and feeding disturbances, and respiratory symptoms may occur both in CMPA and in primary and secondary (to CMPA) GER.[138] CMPA has been reported in up to half of infants presenting with persisting GER.[139,140] Also, the ESPGHAN allergy guidelines from 2012 concluded that the diagnosis of CMPA is likely if regurgitations are frequent and other unexplained symptoms involving at least two different systems are present.[141] In fact, due to the non-specific nature of the GER as a symptom, some researchers propose an empiric trial of a hydrolyzed formula for infants to rule out CMPA.[142] Non-IgE mediated food allergy in early childhood has also been associated with later FGIDs.[110,143]

The role of recurrent, long-term acidic GER in causing dental erosion is unclear. The most recent study by Wild *et al.* states that in children, GER is not associated with dental erosion.[144]

Infant rumination syndrome

In infant rumination syndrome, a child expresses for at least two months voluntary repetitive contractions of the abdominal muscles, diaphragm, and tongue, leading to effortless regurgitation of gastric contents. Onset is usually between the ages of 3 and 8 months. The ruminating child is asymptomatic during sleep and when interacting with other people and does not show signs of distress when ruminating.[13] Limited data on prevalence of rumination syndrome in infants exists.[117] The infant rumination syndrome has been related to emotional and sensory deprivation, but the etiology is most likely multifactorial.[13,145]

Infant colic

Infant colic is defined in the new Rome IV classification as an infant younger than five months cries or fusses for prolonged periods without an apparent cause, is hard to soothe, and crying cannot be prevented or resolved by the caregiver. The infant is otherwise growing well and has no signs of infection.[13] The prevalence of infant colic is estimated to be 5-20% worldwide.[146–148] In most cases, infant colic is a self-limiting condition, and no medical interventions are needed.[149]

In healthy babies, crying is part of normal communication, increasing from birth, peaking at 5-6 weeks of age, and declining around three months of age.[150] Nurturing a hard-to soothe infant is stressful for parents, and they need a lot of empathetic reassurance and guidance. Factors related to maternal depression during pregnancy,[151] partnership, or delivery experiences may harm the infant-mother relationship and influence the risk of extended infant crying.[152–154] Whether fussy and hard-to-soothe infants have abdominal pain (colic) has been discussed.[155]

Abdominal pain in infants and toddlers

Pain is a subjective, unpleasant sensory and emotional experience that involves nociceptive and emotional, cognitive, and social components.[156] In infants, the experience of pain may be more intense than in older children due to at lower pain threshold and decreased ability to modulate pain experiences.[157] Painful experiences in infancy may alter pain processing mechanisms, possibly leading to visceral hyperalgesia. Notably, both physical and psychological stressors have been reported to enhance the perception of visceral pain,[158,159] leading to functional abdominal pain.[160,161] Early life stress is suspected to increase the likelihood of developing a pain-related condition.[162] Currently, there is a lack of instruments for assessing pain in young children.[17]

2.1.4 FGIDs in older children and adolescents

Prevalence

As in infants and toddlers, FGIDs in older children and adolescents are diagnosed using the symptom-based Rome IV criteria for this age group.[1] The prevalences of FGIDs relevant to this dissertation are shown in Table 2.

Table 2:

Prevalences of functional gastrointestinal disorders of the upper gastrointestinal tract in children and adolescents according to the Rome IV criteria.

Disorder	**Prevalence, %**
Cyclic vomiting syndrome	<1
Functional nausea and functional vomiting	unknown
Rumination syndrome	unknown
Aerophagia	4-8
Functional dyspepsia	1-10
Abdominal migraine	1-23
Functional abdominal pain−not otherwise specified	8-15

Modified from Hyams *et al.*[1]

Recurrent abdominal pain

Recurrent abdominal pain (RAP) is defined as episodic attacks of abdominal pain over at least three months that are severe enough to affect the child's usual activity.[1,163] The pathogenesis is unclear but is likely multifactorial. Alterations in gut motility and gut-brain interaction, sensitivity to visceral stimuli, inadequate activation of the immune system, and psychosocial stressors are considered important contributing factors.[164–166]

RAP is a common complaint in children, affecting 20% of the pediatric population,[109,167,168] and in nearly all of these patients no single cause of pain has been identified.[169] The prevalence of pain-related FGIDs in children increases linearly with age, with an approximate 6% increase per year.[16] A recent meta-analysis of prevalence studies found a pooled prevalence of abdominal pain-predominant FGIDs of 13.5% in children aged 4-18 years.[109] These disorders result in high health-care costs and loss of economic productivity for parents/caregivers.[170]

Abdominal migraine

Abdominal migraine is defined as moderate to severe paroxysms of abdominal pain in the midline or periumbilical area combined with headache, nausea, vomiting, anorexia, or pallor lasting for at least one hour before resolving.[1,171,172] The prevalence is estimated at 1-9%, and it is most common in girls aged 3-10 years.[167]

Functional nausea and vomiting

Nausea is described as an unpleasant but painless sensation of imminent vomiting often located in the epigastrium and commonly perceived in the throat or head.[173] The Rome IV criteria define functional nausea as bothersome nausea as the predominant symptom, occurring at least twice per week for at least two months, and it is not meal-related or consistently associated with vomiting.[1] Functional nausea is not associated with pain, which differentiates it from functional dyspepsia. No pediatric data exist on the prevalence of isolated nausea, isolated vomiting, or a combination of both.[1]

Rumination syndrome and aerophagia

Rumination is defined as voluntary regurgitation of ingested food by increasing the abdominal cavity pressure with contracting abdominal muscles. Prevalence in children and adolescents is unknown, and even parents may be unaware that their child ruminates. Psychiatric co-morbidity may be present.[1]

Aerophagia is reported especially in children with neurocognitive disabilities. It is defined as excessive swallowing of air and distension of the abdominal wall, leading to increased belching or flatus for at least

two months. The overall estimated prevalence of aerophagia in children is 4-7%,[1] and it may be associated with anxiety.[174]

Functional dyspepsia

Functional dyspepsia (FD) is defined as either post-prandial fullness, early satiation, or epigastric pain at least four days per month for at least two months. FD is considered one of the pain-associated FGIDs. Depending on the leading symptom, FD can be categorized as post-prandial distress syndrome or epigastric pain syndrome.[1] Etiology is likely to vary, but hypotheses include genetic predisposition, low-grade inflammation, and neural sensitization.[175] FD has been associated with prior acute bacterial gastroenteritis.[176] In the meta-analysis of Korterink et *al.*, the worldwide prevalence of FD in the pediatric population was reported at 4.5%.[109] In FD, there is no acid reflux, nor is there symptom correlation in the combined multichannel intraluminal impedance pH measurement (MII-pH).

Cyclic vomiting syndrome

In cyclic vomiting syndrome, the child must have within six months at least two periods of paroxysmal vomiting stereotypical for each patient, lasting hours to days. Between vomiting episodes, the child returns to normal baseline health and other conditions need to be ruled out.[13] It has been proposed that cyclic vomiting is related to neuronal hyperexcitability in the neural circuits.[177,178] Fleisher *et al.* estimated that cyclic vomiting syndrome may present from infancy to adulthood with a peak incidence between the ages of 2 and 7 years.[179] Hyams *et al.* estimated the median age at onset to be 3.5-7 years and the prevalence 0.2-1.0%.[1] Cyclic vomiting syndrome seems to be more common in girls than in boys (3:2).[180]

2.2. Organic diseases of the upper gastrointestinal tract during early childhood

2.2.1 Gastroesophageal reflux disease (GERD)

Background and pathogenesis

GER is defined as GERD when GER causes troublesome symptoms and complications affecting daily life and functions.[15,21,23,181,182] To date, no gold standard diagnostic tool exists for the diagnosis of GERD in infants and children, rendering the disease definition open to wide variation and heterogeneity. The distinction between physiologic GER and pathologic GERD is often unclear. However, the acidic contents of the stomach are considered to play a crucial role in the development of complications in GERD. Under normal circumstances, the human GI tract's acidity is tightly regulated and varies according to the location. The lowest pH is present in the stomach, with acid helping to dissolve food. The acidity decreases towards the end of the small bowel. The stimulation of acid production is affected by food, stress, and paracrine signaling.[183] During GER the acidic content of the stomach enters the esophagus with or without provoking vomiting. The mucosal layer in the esophagus is not protected against the acid, and acidic refluxate may lead to tissue damage and inflammation.[184] The esophagus is protected from the gastric content by pre-epithelial, epithelial, and post-epithelial mechanisms. A sphincter mechanism consisting of the upper and lower esophageal sphincter (LES) and the crural diaphragm (esophagogastric junction) anatomically separates the esophagus from the stomach. The LES stays contracted during fasting. These protective esophageal guardians relax to allow bolus to proceed from the oral cavity into the stomach during swallowing. If this relaxation occurs without a preceding swallow, it is called a transient relaxation of the lower esophageal sphincter (TLESR). This mechanism is physiological and aids in releasing swallowed air from the stomach, but it also considered the primary cause of regurgitation.[181,185] The different pathogenetic factors in GERD are presented in Table 3.

Table 3 Possible pathogenetic factors in gastroesophageal reflux disease.

1. Dysfunction of the antireflux barrier a) Hiatal hernia b) Lower esophageal sphincter (LES), crural diapraghm c) Transient relaxations of the LES d) Swallow-induced LES relaxations
2. Impaired esophageal clearance a) Decreased secretion of bicarbonate from the saliva and the esophageal glands b) Impaired primary and secondary peristalsis in accordion with the swallowing
3. Gastric factors a) Gastric acid hypersecretion b) Delayed gastric emptying

c) Gastric distension d) Abnormal antropyloroduodenal antireflux; bile, pancreatic enzymes
4. Impaired esophageal mucosal defense mechanisms
5. External factors a) High-fat foods and other dietary issues b) Medications
6. Increased esophageal sensitivity
7. Disturbances of the esophageal microbiota

Modified from Bor.[184]

Prevalence and risk groups

Despite better understanding of the underlying mechanisms, the diagnosis of GERD in children and adolescents remains challenging.[21,186] The disease's reported prevalence rate in children is highly variable, ranging between 5 and 20%.[187–189] Comparison between studies is hindered by the heterogeneity of the GERD definitions and the lack of objective diagnostic criteria and diagnostic tools. Based on the meta-analysis of Singendonk *et al.*, GERD symptoms are present in more than 25% of infants daily and show a steady decline with increasing age. In older children, GERD symptoms are present in >10% of children daily and a quarter of children monthly.[190] However, the reported prevalence of GERD in patients of all ages worldwide is rising.[121] GERD is nevertheless far less common than simple GER. The risk groups for increased GER have also increased risk for GERD.[15,191] In addition, there has been discussion of a relationship between CMPA and GERD. Nielsen *et al.* reported that 56% of children with severe GERD also tested positive for IgE-mediated CMPA on a double-blind or open challenge.[192] However, the role of cow's milk in causing GERD is considered to be limited to young infants.[110]

Symptoms and diagnosis

It has been estimated that children older than eight years of age might be able to recognize and report GER-related symptoms such as heartburn reliably.[121] However, the symptoms attributed to GERD are non-specific, common in a population without GERD, and may resemble symptoms related to other diseases.[21,191]

GERD symptoms have traditionally been classified as esophageal and extraesophageal.[21] The former usually includes vomiting, poor weight gain and feeding problems, irritability, dysphagia, and retrosternal

pain.[15] As extraesophageal GERD symptoms, many researchers and clinical practioners include various respiratory symptoms such as wheezing and laryngitis, infant apnea, and neurological symptoms,[15,122] but the correlation between respiratory symptoms and GERD is insufficient. GERD has also been studied as a cause for brief resolved unexplained events for potentially leading to life-threatening respiratory problems and apnea in infants. These associations have not been proven.[193] GERD has also been associated with the Sandifer syndrome, which is a rare disorder presenting with dystonic spasmodic movements of the head, neck, and back.[193]

There have been many attempts to establish a clinical guideline or a symptom-based score to help evaluate different symptoms attributed to GERD and assess their relationship with GERD complications, but thus far, these have proven unsuccessful.[186] The main problem is the heterogeneity in GERD definition and the chosen outcomes.

The so-called red flag signs listed in Table 4 are alarm features that warrant further consideration and evaluation to exclude diseases other than GERD.

Table 4

Signs and symptoms warranting further evaluation in children with symptoms suggestive of gastroesophageal reflux disease.

General
-weight loss, lethargy, fever, excessive irritability/pain, onset of regurgitation/vomiting after 6 months of age or persisting after 12 to 18 months of age
Neurological
-bulging fontanel, rapidly increasing head circumference, seizures, macro- or microcephaly
Gastrointestinal
-persistent forceful vomiting, nocturnal vomiting, bilious vomiting, hematemesis, diarrhea, rectal bleeding, abdominal distension

Modified from Rosen *et al*.[21]

Combined Multichannel Intraluminal Impedance and 24-hour pH-monitoring (MII-pH)

Traditionally, the acidic burden of the esophagus has been evaluated using 24-hour pH-monitoring. Abnormal acid reflux is defined using acid exposure time. It indicates the proportion of time of the whole monitoring time in which the intraesophageal pH was < 4.0. Acid exposure time >6% is considered positive for pathologic acid reflux.[194,195] A more recent innovation MII-pH uses a catheter with multiple electrodes inserted within the esophagus. Bolus movements are detected through electrical resistance/impedance changes between two segments, and a pH-sensitive electrode monitors acidity. Thus, MII-pH can detect acid, weakly acidic, and non-acid reflux episodes and differentiate anterograde from

retrograde bolus movements.[196–198] The normative MII-pH values in children have only very recently been introduced in the literature.[199]

There have been conflicting results of whether positive MII-pH correlates with positive EGD results. Salvatore *et al.* have stated that MII-pH could not predict which children had histological changes in the EGD. However, the sample size was small (n=45), and at that time, the MII-pH technique had just been introduced in pediatric patients.[200] Hin Lee *et al.* reported no correlation between abnormal MII-pH measurement and positive EGD findings in a small cohort of children (n=45, mean age 6.6 years).[201] However, a study by Hojsak *et al.* reported contradictory results.[202]

GERD phenotypes

Rather than a single disease, GERD is a cluster of syndromes with a complex matrix of contributing pathophysiology.[203] The gut-brain axis may be involved in esophageal symptoms, the gut mucosal injury may cause sensitization and lead to allodynia or hyperalgesia,[204] and physical or psychosocial stress is associated with esophageal hypersensitivity.[205] GERD is divided into subgroups based on EGD findings and MII-pH measurements and their correlation with the patient's symptoms. In addition to erosive esophagitis and non-erosive esophagitis, esophageal hypersensitivity and functional dyspepsia may cause similar symptoms.[207]

Table 5: Phenotypes of disorders related to gastroesophageal reflux symptoms.

Erosive esophagitis (classical GERD)	Visible breaks in the esophageal mucosa during EGD
Non-erosive reflux disease (NERD)	Negative EGD, typical reflux symptoms, abnormal acid exposure and positive symptom correlation in MII-pH
Reflux hypersensitivity acid/non-acid	Negative EGD, typical reflux symptoms, normal acid exposure and positive symptom correlation to either acid or non-acid reflux on MII-pH
Functional dyspepsia	Negative EGD, reflux symptoms that do not respond to acid blockers, normal acid exposure and negative symptom correlation on MII-pH

Modified from Mahoney *et al.* [206]

EGD=esophagogastroduodenoscopy; MII-pH=combined esophageal multichannel intraluminal impedance and 24-hour pH-monitoring

Most adults with GERD have the non-erosive type (non-erosive reflux disease, NERD),[208] but the clinical features of NERD in children have only been reported in recent years.[206,207] Mahoney *et al.* investigated the reflux phenotypes in children and reported functional dyspepsia as the most common phenotype at 44%. Histological esophagitis did not correlate with any reflux phenotype and no difference in anti-acid medication responsiveness between different phenotypes emerged.[207]

Respiratory symptoms as signs of GERD

The association between GERD and various upper and lower respiratory tract problems has been widely discussed in the literature. As early as in the 1960s, Kennedy introduced a concept of "silent reflux," referring to situations where GER was considered to cause only respiratory symptoms.[209] Harding *et al.* presented a small prospective study in 2000 of asthma patients without clinical GER symptoms with ambulatory pH-monitoring and found that 62% of asthma patients had acid GER of which they were unaware.[210] El-Serag *et al.* noted in a large case-control study that children with GERD have significantly more sinusitis, asthma, and pneumonia. In their cohort, they had excluded children with cerebral palsy, mental retardation, or tracheoesophageal malformations. However, GERD's diagnosis was only set via diagnosis search, and the presenting symptoms leading to the GERD diagnosis were not discussed. Also, no data existed on possible EGD findings and esophagitis or on any medications used.[211]

Lack of a gold standard diagnosis in GERD has also challenged performing systematic reviews and meta-analyses on the association of asthma with GERD in the pediatric population.[212] Rosen *et al.* performed a prospective study on children (mean age 6.1 years) with prolonged respiratory symptoms such as cough, wheezing, asthma, and recurrent pneumonia. The patients underwent concurrent MII-pH, bronchoscopy, and EGD. The authors reported abnormal results in at least one of these diagnostic measurements in 58% of the 112 children. However, only one in four parents reported that PPI medication had relieved the child's supposedly reflux-related respiratory symptoms. The authors also stated that they did not find any evidence of gastric contents in the bronchoalveolar lavation samples taken during bronchoscopy.[213] Recently, de Benedictis and Bush performed a meta-analysis of suspected GERD-related respiratory manifestations and concluded that GER neither causes nor results from asthma, and that the causality of GER in cough or laryngopharyngitis in children is not proven. In generally healthy children with cough, empirical PPI treatment is likely ineffective and is not recommended.[214]

Endoscopic manifestations of GERD

When GER-related endoscopic changes are present, esophagitis can be divided into erosive and non-erosive types. In erosive esophagitis, damage to the esophageal mucosa is readily seen, and changes are traditionally classified using the Los Angeles grading.[215] In children, the prevalence of erosive esophagitis is low.[22,216] In a study by Gilger *et al.*, only 12.4% of children who underwent an EGD because of suspicion of GERD complications such as esophagitis had erosive esophagitis. The incidence rate for erosive findings significantly increased with age.[22] However, Del Giudice *et al.* studied children with cerebral palsy (aged 0.5-12 years) and reported that 91% of the children with symptoms suggestive of GERD had either esophagitis or abnormal 24-hour pH-monitoring. Most of the children with histological esophagitis (79%) had moderate to severe histological esophagitis.[217]

Symptoms do not correlate with erosive findings in the EGD. In a study by Gupta *et al.*, no differences in symptoms emerged between children with erosive and non-erosive esophagitis.[23] In adult patients, esophageal biopsies can assist differential diagnosis,[182] but in children reflux phenotypes do not differ according to the possible histological esophagitis.[21,207]

Microscopic esophagitis has been defined as the presence of eosinophils, papillary lengthening, and basal cell hyperplasia.[218] The relevance of low-grade histological findings is unclear, and such mucosal changes are found also in asymptomatic controls.[182,219] The pathologist interpreting the biopsies must be familiar with esophageal pathology and experienced to assign reliable histopathological diagnoses.[220] The histologic features in GERD are non-specific, as they reflect a general pattern of injury, not a specific entity.[24]

In addition to esophagitis, in patients with GER, the histological examination may reveal a shift in the lower esophagus' normal squamous epithelium to a specialized intestinal epithelium. This change is also called the Barrett esophagus, which is considered a metaplastic, premalignant change.[221] The incidence of Barrett changes has been shown to increase in adulthood, and risk factors mentioned are long-standing GERD (either erosive or non-erosive), male gender, obesity, and age over 50 years.[222] Even though acid reflux is considered a major risk for developing intestinal metaplasia, the etiology is not fully understood.[221,223] However, Barrett changes are very rarely found in children.[224,225]

Esophageal microbiome in health and disease

Microbiome research has focused mainly on the intestinal microbiome, as collecting stool is a convenient way to gain research samples. However, also some studies involving the esophageal microbiome exist. Previously, the esophagus was considered to lack a significant bacterial population, but 16S rRNA gene sequencing and minimally invasive microbial sampling methods have facilitated characterization of the esophageal microbiome.[226,227] Acidity of the proximal GI tract is essential to the local microbiome composition.[228] *Streptococcus* is reported as the most common bacteria in a normal, healthy adult esophagus.[229] Gram-negative lipopolysaccharide producing bacteria, such as *Escherichia coli* have been associated with delayed gastric emptying, decreased LES tonus, and disturbed barrier function of the esophageal mucosa.[226] There has been only one pediatric study exploring the esophageal microbiota by Fillon *et al.*, reporting the genera *Streptococcus*, *Prevotella*, and *Veillonella* as the most common phyla.[230]

Treatment

Anti-acid medication has been widely used to treat perceived or suspected reflux-related symptoms empirically. The first available group of medicines was histamine 2 (H2) receptor antagonists. Nowadays, the most commonly used medication is PPIs, which act by blocking the gastric H+/K+ -ATPase, thus inhibiting gastric acid secretion.[231] Recently, an understanding of the side-effects of acid suppression has

emerged. Necrotizing enterocolitis and late-onset sepsis in preterm infants have been associated with ranitidine, an H2 receptor antagonist treatment.[232,233] Most of the anti-acid medication currently used is PPIs, and the user numbers have been expanding rapidly.[234] In addition to the side-effects and risks, the benefits of PPI medication use in infants are low [235–237]. PPI use in infants has been cited as one of the top 20 low-value pediatric services in the USA that typically do not improve child health.[238]

Adult studies report that PPIs alter the gut microbiota in a non-desirable direction. The numbers of oral origin bacteria and pathogens increase.[68] Levy *et al.* focused on the effect of PPI medication on the microbiome in a pediatric age group. They concluded that PPIs are associated with adverse effects such as necrotizing enterocolitis, late-onset sepsis in preterm, *Clostridium difficile* infection, small intestinal bacterial overgrowth, asthma, and obesity.[239] In a study by Schwartz *et al.*, early infancy PPI and H2 antagonist use were associated with an increased risk for IBD.[240] Also, Trikha *et al.* showed that children exposed to anti-acid medications (H2 or PPI) due to GERD symptoms were twice as likely to be diagnosed with food allergy after a year of treatment as healthy controls or children with non-pharmacological treatment for GERD.[241]

Despite all of this evidence, a study by Savarino *et al.* did not confirm any specific harms related to prolonged PPI use in the adult population. They stated that previous studies have been observational, and thus, prone to bias and false interpretations.[242] However, a similar review in the pediatric population by de Bruyne *et al.* noted that the safety profiles of pediatric PPI use are inconclusive, and PPI use in children should be reserved for cases of severe (acid) GERD and gastric bleeding.[243]

Prokinetic medication has been recommended as a treatment option for adult patients who fail to respond to PPI therapy.[244] Especially cisapride has been used to improve gastric motility also in children, but evidence supporting the use in GERD is lacking.[245] Also, cisapride has been taken off the market due to cardiac side-effects.

Surgical treatment has been considered as a treatment option for GERD, particularly in children with neurological or other underlying conditions. In such children, Koivusalo *et al.* reported 90% symptom control after a primary fundoplication.[246] The role of fundoplication in otherwise healthy children with troublesome GERD is unclear.[247]

Quality of life

The importance of health-related quality of life (HRQoL) has been acknowledged widely in the pediatric population within the last 20 years. HRQoL refers to not only how symptoms affect the individual but how the disease impacts psychosocial, mental, emotional, behavioral, and school functioning.[248] In children with GERD, the HRQoL has been reported to be significantly decreased, even when compared with children

with IBD.[249]. In addition, the decrease in QoL is not associated with the amount of acid reflux burden measured with MII-pH.[250]

Prognosis

The prognosis of childhood GERD is unclear. Singendonk *et al.* performed a systematic review of prognosis and prognostic factors in otherwise healthy children with GERD[251] and found only four suitable articles.[252–255] These studies are heterogeneous, and based on them, no conclusions about the prognosis of GERD in the pediatric population can be made.

2.2.2 Inflammatory bowel disease

Background and pathogenesis

Inflammatory bowel disease (IBD) is characterized by a chronic, remittent, and relapsing inflammation in the GI tract possibly due to an exaggerated immune response to gut microbiota in genetically susceptible individuals.[256–259] The two major forms of IBD are Crohn's disease and ulcerative colitis, defined by clinical, histological, endoscopic, and radiological features.[260] Children who develop IBD at a noticeably young age are a very distinct subgroup of IBD patients. These infants and toddlers may have atypical disease presentation with faltering growth and extensive colitis called unclassified IBD with poor response to conventional drug therapies.[261] The Paris classification of childhood IBDs defines early-onset IBD as a disease diagnosed in children younger than 10 years.[262]

The pathogenesis of IBD remains incompletely understood.[257] The association between changes in the gut microbiota and IBD has been recognized for some time.[54] Factors that shape the microbiota including early childhood exposure to antibiotics,[263] are suspected to increase the risk of IBD. Patients with IBD have characteristic gut microbiome patterns[264–266] and the bacterial taxa have altered from what is considered healthy or normal.[267–270] The extent of dysbiosis is associated with the disease severity.[257] Recently, Kolho *et al.* demonstrated a correlation between reduced microbial richness and a higher inflammation level in a Finnish patient cohort.[271]

Prevalence

For several decades, starting in the 1950s, a marked increase in the prevalence of IBD was observed in Western countries, but the prevalence reached a plateau in the 1990s. A similar increase in prevalence has been seen in many newly industrialized countries, adopting a westernized lifestyle.[26,272] The general onset of IBDs peaks in late adolescence and early adulthood.[28] Previously, IBDs were considered rare in children, but now they are global diseases affecting children in developed and developing countries.[25,273] In Finland, Virta *et al.* reported an average increase rate of 4.1% in pediatric IBD prevalence in 2000-2014, but there was no significant increase in prevalence among the youngest age groups.[27]

Symptoms and diagnosis

In children diagnosed with Crohn's disease, the most common symptoms were abdominal pain, weight loss, diarrhea, and growth retardation. In ulcerative colitis and unclassified IBD, the most typical symptoms include diarrhea, bleeding, and abdominal pain.[274,275]

The diagnosis of IBD relies on endoscopy findings.[28] Crohn's disease's histopathology is characterized by often discontinuously appearing transmural granulomatous inflammation that can affect any part of the GI tract. By contrast, ulcerative colitis is limited to the colon, and histopathology shows superficial mucosal ulceration. Pediatric ulcerative colitis often has a severe disease course, and the number of patients requiring

colectomy is higher than in adults.[276] Unclassified IBD is a chronic colitis that lacks the distinguishing features of either Crohn's disease or ulcerative colitis.[258]

2.2.3 Eosinophilic esophagitis

Background and pathogenesis

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated esophageal disease characterized by symptoms of esophageal dysfunction and histologically by eosinophilic inflammation.[31,277,278] After a few studies in the adult population, Kelly *et al.* described in 1995 a series of 10 infants and toddlers who had difficult GERD-like symptoms and a remarkably high number of eosinophils in esophageal biopsies (median of 41/HPF). The children did not respond to conventional reflux treatment but improved when fed solely an amino acid formula.[279] After these findings, EoE has been diagnosed increasingly in all age groups, but the incidence has significantly increased among school-aged children and adolescents.[280–283] The pathogenesis remains unknown, but more than two-thirds of patients with EoE are either atopic or sensitized to a food antigen.[284,285] The most common food antigens in EoE patients are milk, wheat, egg, and soy.[32,285] In pediatric patients, the role of aeroallergens seems to be smaller than in adults.[286] However, at recent systematic review states that current allergy testing methods are not sufficiently accurate to provide all the necessary information on food allergens.[285]

Prevalence

EoE affects more often male patients (male-female ratio of 2:1-3:1).[32,284] Arias *et al.* conducted a population-based meta-analysis and estimated the pooled pediatric EoE prevalence at 34 cases per 100 000 inhabitants (95% CI 22.3-49.2).[287]

Symptoms and diagnosis

In children, feeding intolerance and difficulty in swallowing are considered signs of esophageal dysfunction. However, in younger children, symptoms are often non-specific. The mean age at diagnosis is 6-7 years.[285]

EoE diagnosis is based on esophageal biopsies. The eosinophil count must be ≥15/high-power field in at least one esophageal biopsy. Multiple biopsies enhance the possibility of attaining at diagnosis.[30,288] Also, other conditions that might mimic EoE should be ruled out.[289] The number of eosinophils in swabs available from the pharynx or upper airways do not correlate with eosinophil load in the esophagus, and swabs cannot be used as a diagnostic tool.[290] A novel diagnostic approach is based on the patient's symptoms. Martin *et al.* have validated a new questionnaire, The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS version 2.0). They found that parents effectively capture relevant symptoms and

that the dysphagia domain provides the best information on symptom versus tissue-based molecular marker correlation.[291] The role of allergy testing in identifying foods that lead to EoE is controversial.[285]

2.2.4 Food allergy with gastrointestinal symptoms

Background and pathogenesis

Food allergy is common in childhood and presents with adverse health effects after exposure to food.[141] Food allergy develops when the immune system reacts against food antigens.[292,293] One of the most common food allergies in infants and young children, with a prevalence of 2-5%, is CMPA.[292,294–297] The allergic reaction may arise via specific immunoglobulin (Ig) E-mediated, non-IgE-mediated (cellular), or mixed immune responses, and involves most frequently the skin and GI tract.[141,298,299] In cow's milk, the major allergens are whey proteins and especially β-lactoglobulin and caseins.[300]

In patients with GI-CMPA, cow's milk allergen-specific IgE antibodies and skin reaction to cow's milk proteins are negative. These non-IgE-mediated reactions include food protein-induced enterocolitis syndrome (FPIES), cow's milk protein-induced enteropathy, and cow's milk-induced proctitis/proctocolitis.[298,301]

Prevalence

Only average estimations can be made on prevalence of GI-CMPA, but the reported prevalence of food challenge proven non-IgE CMPA is 0.6%.[296] The prevalence of parentally perceived cow's milk-related GI symptoms is markedly higher.[302]

Symptoms and diagnosis

In a non-IgE-mediated allergic reaction, the allergic reactions may manifest up to 48 hours or even longer after ingestion.[141] Symptoms vary according to the organ involved, but in the GI tract allergic reactions may include regurgitation and vomiting, dyspepsia, food refusal,[141] failure to thrive,[192] diarrhea or rectal bleeding,[303] abdominal pain and severe colic,[304] and even persistent constipation.[305] Non-specific symptoms, such as fussiness or prolonged crying, have not been associated with non-IgE CMPA.[306] In view of the various symptoms overlapping with FGIDs[122,141] and the potential delay of symptoms, the clinical diagnosis is not straightforward. The gold standard to diagnose a non-IgE food allergy is the double-blind, placebo-controlled food challenge (DBPCFC).[36,307,308] In a study by Merras-Salmio *et al.*, the most common symptom related to non-IgE mediated CMPA in infants was loose stools, occurring

in 78% of DBPCFC-positive children.[38] However, since GI symptoms during infancy are common, it is likely that some of the positive reactions even in the DBPCFC are false.[146,309]

A subgroup of young children manifesting with non-IgE food allergy with GI symptoms has a more severe disease course. FPIES is a cellular, non-IgE-mediated allergy to food that typically manifests in infants less than one year of age.[310,311] FPIES may present in acute or chronic form.[312] The symptoms in acute FPIES are prominent and include forceful vomiting with lethargy that may lead to dehydration.[313] Watery diarrhea may follow the acute reaction within 24 hours. Measurable laboratory findings include neutrophilia, eosinophilia and thrombocytosis, metabolic acidosis, and methemoglobinemia.[35] The phenotype of chronic FPIES is characterized by intermittent but progressive emesis and watery diarrhea with mucus and occasional blood. In infants, diarrhea predominates. This often leads to failure to thrive (FTT), hypoalbuminemia, and metabolic derangements.[311,314] Food challenges in children with suspicion of FPIES are performed as open.[315]

Prognosis and quality of life

Prognosis of food allergy depends on the type of allergic reaction that the culprit food induces. Generally, IgE-mediated reactions tend to persist longer than non-IgE-mediated reactions.[137] The prognosis of non-IgE-mediated cow's milk allergy is good, with approximately half of affected children developing tolerance within the first year, and nearly all tolerate cow's milk protein at six years of age.[141,299] Food allergy has been associated with reduction in QoL.[316] Parent-proxy reports on the child's QoL improved significantly after a food challenge in children aged 0-12 years, and larger improvements in QoL were shown after a negative outcome than after a positive outcome.[317]

2.3 Esophagogastroduodenoscopy (EGD)

Background

Pediatric EGD started in the 1970s. The first indications were mainly related to GI bleeding.[318] Following technical innovations, the number of pediatric first-time EGDs has been on the rise.[41,42,319,320] As pediatric EGD has become widely available,[39] the rapidly increasing number of EGDs performed has led to discussion on cost effectiveness.[42]

The key differences between pediatric and adult diagnostic procedures are that in children EGDs are usually performed under sedation or general anesthesia. Also, routine biopsies are recommended from at least the duodenum, the stomach, and the esophagus due to the poor correlation of macroscopic and histological findings.[321–324] However, most pediatric EGDs are reported to yield a negative result,[40–42,325] and different combinations of symptoms, risk groups and questionnaires have been evaluated in hopes of finding a tool that could help identify patients with positive EGD outcomes. Lyons *et al.* reported that patients age

(≥12 years), African American race, dysphagia, and positive celiac antibodies are significant independent predictors of a positive EGD outcome.[326] Known risk groups for erosive esophagitis are children with congenital malformations of the GI tract, neurodevelopmental issues, chronic pulmonary conditions, and muscle dystrophies.[121,135,136,327,328]

Macroscopic evaluation

Macroscopic evaluation refers to the appearance of the GI mucosa during endoscopy. This evaluation is subjective, although guidelines and classifications exist to give better consistency to the diagnosis. Here, only mucosal findings relevant to the population included in this study are addressed.

In children, the most common mucosal damage is related to GERD. Reflux-related macroscopic esophageal findings are often classified using the Los Angeles grading system. This validated system was primarily developed for adult use and describes the appearance of the mucosa according to the abnormal features observed. The classification ranges from A (at least one mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds) to D (at least one mucosal break that involves at least 75% of the esophageal circumference).[215] Some studies in pediatric populations using the Los Angeles grading system are available, and the classification seems to suit pediatric purposes.[327] Macroscopic changes can also be described as erosions, ulcers, strictures, or their combinations.[329] In adult studies, grade A-B erosive changes have been found in asymptomatic controls as well, and are often considered non-specific.[330]

Thin mucosal protrusions known as webs and rings may be detected during EGD. Webs are usually located in the upper and middle esophagus,[331] but rings often occur in the lower esophagus. Rings are frequently seen in association with EoE.[332,333]

Esophageal inlet patches are mucosal lesions of variable size and salmon-pink color,[331] and the incidence in pediatric patients undergoing EGD because of non-acute symptoms has been estimated at 1.4%.[334]

Esophageal candidiasis may manifest in EGD as white plaques either focally or confluently and an apparently inflamed underlying mucosa.[329] The appearance may mimic EoE.

Histological evaluation

The location of the biopsy in the esophagus is relevant. For instance, few eosinophils seen within a couple of centimeters upwards from the gastroesophageal junction can be considered a normal reaction to physiological GER.[335] The most common way to take tissue samples during the EGD is to use pinch biopsy. This enables visual control of the biopsy location. After the biopsy is detached from the tissue, it is placed in a container with fixative, most commonly formalin. The size and number of the biopsy are relevant

for the histological diagnosis.[336] Moreover, the clinical information for the pathologist is important since many histological findings are non-specific.[329]

Inflammatory lesions of the esophagus include eosinophilic and lymphocytic esophagitis, reflux-related esophagitis, chemical esophagitis due to chemical irritation (pills, other noxious agents) and infectious esophagitis.[24]

In GERD, the acidic content of the stomach induces a non-specific tissue injury to the esophageal mucosa. The histological features of GERD esophagitis include basal cell hyperplasia, elongation of the lamina propria papillae, increased number of intraepithelial eosinophils, lymphocytes, and neutrophils as signs of inflammation and dilated intracellular spaces reflecting increased paracellular permeability. In addition, intercellular edema and epithelial necrosis may be present.[329] However, in an adult study by Schindlbeck *et al.*, similar findings were made also in healthy, voluntary controls.[337] In fact, as Kruggmann *et al*. stated, the typical histological features of GERD described above are based on the papers written in the early days of endoscopy and might warrant re-evaluation.[218]

In children, the presence of eosinophils is considered a significant finding. According to previous research, eosinophils are not normally present in the mucosa during childhood.[338–341] The major histological features of EoE include the presence of ≥15 eosinophils/HPF under a light microscope, eosinophilic micro abscesses, localization of the eosinophils in the outer layer of the epithelium, surface sloughing of epithelial cells mixed with a large number of eosinophils and extracellular eosinophilic granules.[288,329] The distribution of the disease findings is pathognomonic as EoE may present as patchy focal lesions in multiple sites from the proximal esophagus to the gastroesophageal junction.[329] Due to patchy appearance of EoE, multiple biopsies enhance the probability of attaining a diagnosis.[31,278] The serum IgE level may be elevated, facilitating differential diagnosis.[329]

Crohn's disease may present in the upper GI tract. Usually, minor lesions are found in patients with previously diagnosed Crohn's disease and the prevalence has been estimated at 0.2-11%.[342] Mucosal biopsies show non-specific inflammatory infiltrates with all types of inflammatory cells, as well as inflammatory granulomas.[329]

Esophageal candidiasis (mainly caused by *Candida albicans*) may occur in immunocompetent patients after use of anti-acid medication,[343] or inhaled corticosteroids,[344] and rarely in otherwise healthy patients. A recent study in an adult population reported that *Candida* findings in esophageal biopsies should always be considered pathological.[345]

Pill-induced esophagitis is rare in infants and young children since medications in this age group are usually given in liquid form.

Sheiko *et al.* and Volonaki *et al.* have addressed the diagnostic yield of pediatric EGD biopsies and report the lowest number of histological findings among infants. Also, most of the children with GER-related symptoms have normal findings.[319,322]

EGD safety

EGDs have few absolute contraindications, but relative contraindications include coagulopathy, neutropenia, and unstable cardiopulmonary disease.[346]

The most mentioned adverse events for EGD in children are aspiration, allergic reaction, hypoxia related to sedation/anesthesia, perforation, bleeding, and infection.[347] Thakkar *et al.* reported an immediate procedure-related complication in 2.3%, and as the major subgroups hypoxia in 1.5% and bleeding in 0.3%.[347] In addition, Dar *et al.* noted young age, higher ASA Physical Status Classification score, and intravenous sedation as risks for developing complications.[348] Kramer *et al.* reported a general EGD procedure related adverse event incidence of 2.6% within 72 hours of EGD, but only 1.7% of the cases required additional medical evaluation.[349]

For children with pre-diagnosed long-term illnesses, there are specific guidelines available concerning the procedure-related risks.[350] In general, children require larger doses of sedation medication per weight relative to adults, thus making children more prone to sedation-related side effects.[351] In recent decades, the neurotoxicity of anesthetics in young animals has led to discussion of potential long-term adverse effects of early life anesthesia in children. In human studies, the role of anesthetics as an additional risk for neurodevelopmental disorders has not been proven. The study by Lin *et al.* reported an association of anesthesia exposure and subsequent learning disabilities in young children.[352] Wilder *et al.* investigated a large population-based cohort of children without mental retardation, the risk for learning disabilities was significantly increased in children exposed to two or more anesthetics.[353] Another study on the same birth cohort reported that exposure to multiple but not single anesthetics before the child's third birthday was associated with an increased prevalence of learning disabilities and attention deficit hyperactivity disorder.[354] However, single anesthesia in children younger than three years of age is considered relatively safe.[355]

2.3.7 Guidelines for EGD

The ESPGHAN has recently updated their guidelines concerning use of EGD in children.[356] The consensus committee recommendations on EGD indications are shown in Table 6. It is noteworthy that this recommendation comes with the phrase “weak recommendation, low quality of evidence”.[356] This indicates that research on EGD indications in children warrants further studies. The American Society for Gastrointestinal Endoscopy (ASGE) also provides guidelines regarding pediatric endoscopies,[346] and NICE guidelines aid in the diagnosis of GERD.[357] These guidelines are in line with the ESPGHAN guidelines.[356]

Table 6

The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) consensus committee recommendations for esophagogastroduodenoscopy indications in children.

Indications
Weight loss, failure to thrive
Unexplained anemia
Abdominal pain with suspicion of organic disease
Dysphagia or odynophagia
Recurrent vomiting with unknown cause
Hematemesis
Suspicion of graft versus host disease
Gastrointestinal allergy
Chronic GERD to exclude other diseases or surveillance of Barrett esophagus
Suspicion of IBD

Modified from Thomson *et al.*[356]

GERD=gastroesophageal reflux disease; IBD=inflammatory bowel disease

Lee *et al.* found that the rate of positive histological findings increased by following the ESPGHAN guidelines, but the initial diagnosis or treatment effect was less affected.[43] Thakkar *et al.* conducted a prospective study with children aged 4-18 years who underwent a primary EGD because of chronic abdominal pain. They reported a diagnostic rate of 38%, and the most common findings were GER- and EoE-related.[358] by contrast, Hyams *et al.* stated that EGD was not contributive in a cohort of young children with such symptoms as abdominal pain, vomiting, and nausea, and that most of the symptoms resolved with time without further care or investigations.[359]

Recent consensus statements on FGIDs have taken a more conservative approach to invasive testing. The Rome IV committee no longer support invasive testing in children with likely FGID.[1] Bonilla *et al.* reported that a negative EGD did not lessen subsequent symptoms in children with abdominal pain.[360]

There are no national guidelines in Finland for EGD use in children or referral guidelines concerning EGD criteria in children with non-acute, non-specific symptoms.

3 Aims of the study

This thesis consists of three studies, hereafter referred to as Studies I, II, and III.

Study I investigated which symptoms and indications had led to primary EGDs in children younger than seven years, the EGD results and the impact of EGD results on patients' subsequent care.

Study II further defined the diagnostic process of symptoms suggestive of GERD, the most common indication for primary EGD in this cohort. The aim was to obtain data on follow-up outcomes of symptoms suggestive of GERD in early childhood to fill in gaps in current knowledge.

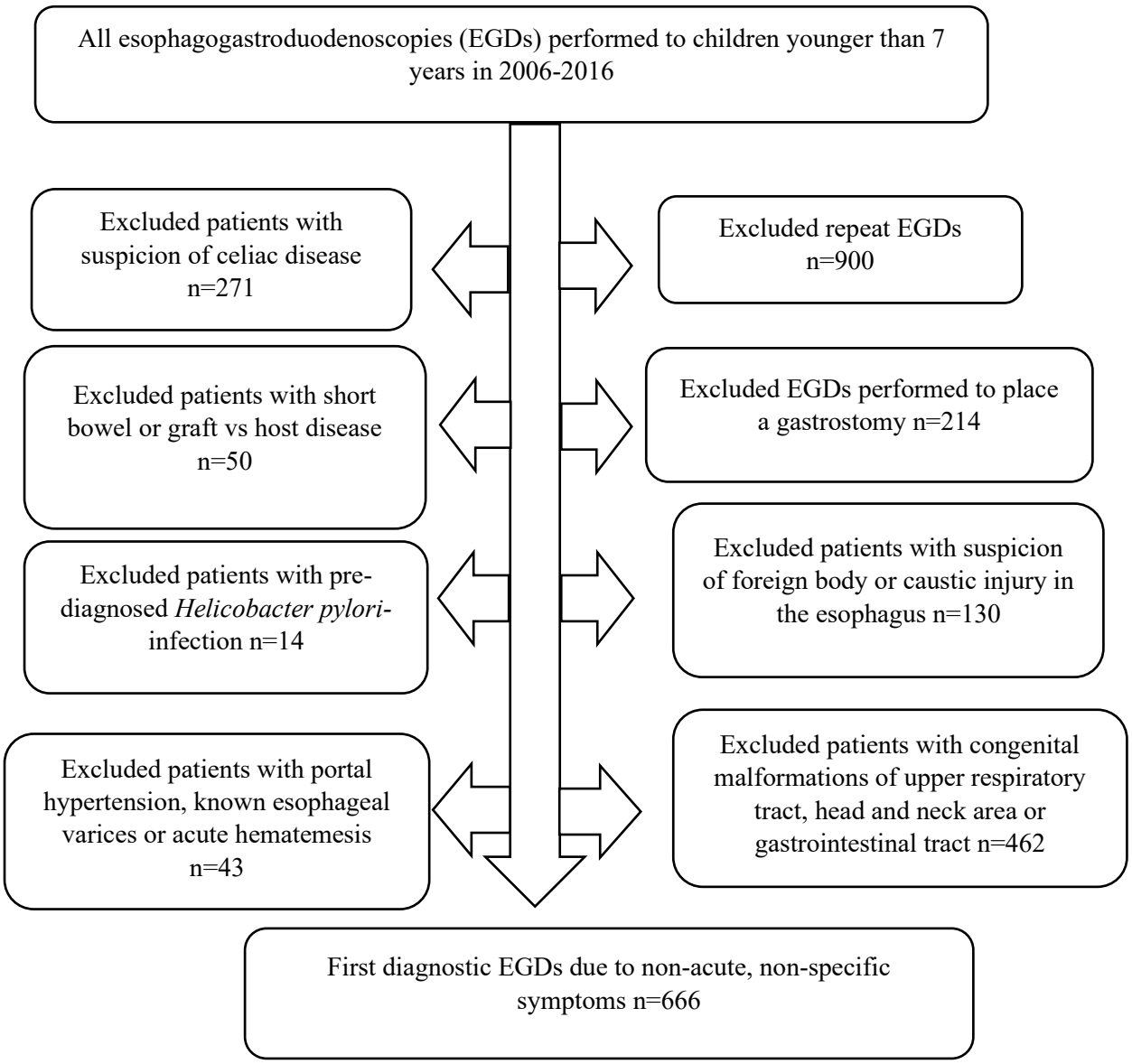
Study III provides follow-up data on patients investigated in infancy using a double-blind, placebo-controlled food challenge due to suspicion of GI-CMPA.

4 Subjects and methods

4.1 Patients and study population (I-III)

For Study I, a data search using the Nordic classification code for surgical procedures UJD-10 was performed to identify all EGDs performed at Children's Hospital in Helsinki, Finland in 2006-2016. Only children younger than seven years were considered (n=2750). Some patients had undergone several EGDs during the period of interest. For this study, only the first diagnostic EGD per patient was included (n=1850). Patient selection with exclusion criteria is shown in Figure 1. The remaining 666 patients formed the population for Study I.

Figure 1 Patient selection for Study I.



Patients who had undergone the primary EGD to diagnose or rule out a GER-related esophagitis were identified in Study I (n=268). Fourteen patients were lost to follow-up, and thus the initial cohort comprised 254 children. Follow-up outcomes of patients with normal findings in the primary EGD (n=199) were further characterized for Study II, and of these, patients with Finnish as their native language (n=175) were invited to an electronic follow-up survey.

In Study III, the study population had participated as infants in a previous research project that had investigated GI-CMPA. In the initial study, infants (n=57) had been referred to an allergy clinic and had been recruited to participate in a prospective study, including a DBPCFC for cow's milk. The symptoms were non-specific, and no one had symptoms suggestive of FPIES. The study protocol is described in more detail in the article by Merras-Salmio *et al.*[38]. In most of these children (68%), the DBPCFC had yielded a negative result. Five years later, mothers of participants of the initial food challenge study were invited to participate in a follow-up study, and their children became the population of Study III. Among the participants were two mothers whose child had also undergone an EGD because of non-specific GI symptoms during the follow-up after a negative food challenge. Therefore, two children were included in both cohorts for Study I and Study III.

4.2 Methods

Retrospective chart review (I,II)

For Study I, the patient records of the identified 666 children were reviewed. Data were collected on patient demographics, symptoms leading to EGD, macroscopic appearance of the upper GI mucosa during endoscopy, and histological diagnoses from biopsies. Also, the impact of EGD findings on the patient's subsequent care was noted. Length of the follow-up period, and new diagnoses, treatments, or interventions during that period were reviewed. The children were divided into three age groups: infants younger than one year (n=122), toddlers aged 1-2.9 years (n=230), and children aged 3-6.9 years (n=314).

For Study II, the patient charts of the 254 children with initial suspicion of GERD were again reviewed, and more detailed information on other reflux-related diagnostic measures performed and endoscopy data were collected. Data on 24-hour pH-monitoring were reviewed, as were co-existing conditions and parentally reported eating-related problems. The total number of EGDs per patient and results of the repeat EGDs were recorded.

For Study III, no chart analysis was performed.

4.2.2 Registry data (II)

For Study II, a data search of the Patient Data Repository and Prescription Service was performed for all 254 patients. In the follow-up, the number of contacts with the health-care system addressing upper GI complaints was noted, and all prescriptions written over the previous two years were reviewed.

4.2.3 Follow-up surveys (II, III)

Follow-up surveys used in Studies II and III were conducted using a secure internet-based questionnaire. The invitation to participate was sent by mail. In Study II, three rounds of invitation letters were sent to families who had noted Finnish as their native language in January-February 2020, but the families were not otherwise personally contacted according to the ethics board's current recommendation. In Study III performed in 2016, a registered nurse had telephoned the invited mothers after sending the invitation letter in the mail and enquired whether they wished to participate.

The questionnaire in Study II included a study-specific section addressing current GER symptoms and anti-acid medication use. All parents and all children older than eight years were invited to fill in the PedsQL GI Symptoms Scales, Finnish version, which had been professionally translated to and validated in Finnish for this study. The questionnaire was validated initially in certain age groups,[361] and the questionnaire was used in this study in an age-appropriate manner.

In Study III, a study-specific questionnaire addressing current GI symptoms, medications, and diet restrictions was used. The mothers also filled in a Finnish version of the PedsQL General Score 4.0 to assess the QoL and the Parenting Stress Index (PSI) questionnaire to address stress related to parenting. Both questionnaires have been validated in pediatric patients[362,363] and are widely used. The mothers had answered the same PSI questionnaire in the previous food challenge study when the children were infants, and the results were compared. In Study III, a comparison of responses of early responders and late responders was performed to assess non-responder bias.

4.3 Statistics

Data are shown as the number of cases with medians and interquartile ranges (IQR) or percentages. Differences between the groups were compared using Fisher’s exact test, and differences among continuous variables were compared using Mann-Whitney U-test. The statistical calculations were performed using GraphPad Prism versions 7.01 and 8.01 for Windows (GraphPad Software, San Diego, CA, USA). Statistical significance was set at $p<0.05$.

4.4 Ethical considerations

The study was conducted according to the principles of the Declaration of Helsinki. The Helsinki University Hospital Ethics Committee approved all studies (Study I: HUS/3668/2017, Study II: HUS/1743/2019, Study III: 13/13/03/03/2016) as required for doctoral research. In Studies II and III, informed consent was obtained

from all parents participating in the follow-up surveys. Also, all children who returned the PedsQL GI Symptoms Scales self-report provided informed consent. According to Finnish legislation, informed consent is not required for register-based studies.

5 Results

Diagnostic yield of primary EGD (I)

Children (n=666) undergoing the primary EGD because of non-acute, non-specific symptoms were a median age of 3.5 years (IQR 1.5-5.2) and 57.7% were boys. Altogether, 40.1% of patients had previous diagnoses such as allergy, asthma, non-GI congenital syndrome, or FGID. Data on allergies were available for 641/666 patients (96.2%). CMPA was earlier diagnosed either using a food challenge (open or double-blind) or by measuring serum levels of cow's milk-specific IgE antibodies in children with allergy-related symptoms (65/641 patients, 10.1%). In 49/65 patients (75.4%), the allergy type had been deemed non-IgE. Detailed patient demographics are described in Table 1 in Study I. Data on growth at the time of primary EGD were available in 641/666 patients (96.2%). In 493/641 children (76.9%), growth was reported as normal.

The main indications for EGD were a suspicion of GERD (n=268), differential diagnosis of various respiratory symptoms (n=120), and suspicion of IBD (n=107) (Table 7). The most common symptoms leading to the primary EGD were perceived as GER-related (food refusal, spilling, vomiting, nausea, burping, swallowing, heartburn, and epigastric pain n=236). The second most common symptoms were various non-specific respiratory symptoms (wheezing, laryngeal, another type of cough, recurrent pneumonia, and obstructive bronchitis n=136), and the third most common symptom was bloody stool (n=115). Among infants, the most common symptoms leading to EGD were various respiratory symptoms (52.5%), and among toddlers and older children GER-related symptoms (48.7% and 43.0%, respectively). The mean length of the symptomatic time was in infants four months, in toddlers 13 months, and in older children 12 months. There was no single symptom or combination of symptoms that predicted positive EGD findings.

Table 7

Data related to primary esophagogastroduodenoscopy (EGD) in 666 children younger than seven years presenting with non-specific, non-acute symptoms.

	Age 0-1 year	Age 1-2.9 years	Age 3-6.9 years
Number of patients	122	230	314
Gender male/all (%)	74/122 (61)	149/230 (65)	161/314 (51)
Indication for EGD n (%) in each age group):			
Suspicion of GERD n=268	38 (31)	100 (44)	130 (41)
Common respiratory symptoms n=120	41 (34)	59 (26)	20 (6)
Suspicion of IBD n=107	2 (2)	25 (11)	80 (26)
Hematochezia (non-IBD) n=50	6 (5)	13 (6)	31 (10)
Exclusion of anatomic abnormality n=33	24 (20)	4 (2)	5 (2)
Dysphagia n=16	0	4 (2)	12 (4)
Failure to thrive n=15	6 (5)	8 (4)	1 (1)

GERD=gastroesophageal reflux disease; IBD=inflammatory bowel disease

Anti-acid medication at time of EGD

Data on anti-acid medication use at the time of EGD were available for 96% of the children, and nearly all of them had a minimum two-week anti-acid medication-free period before the EGD.

EGD findings

All EGDs were performed under general anesthesia using size-appropriate endoscopes. Routine biopsies from the duodenum, the stomach, and the esophagus were obtained in 644/666 EGDs (96.7%) regardless of the macroscopic appearance. The macroscopic appearance was normal in 626 patients (94.0%). No one had erosive macroscopic changes. Of the 22 non-biopsied patients (18 infants, one toddler, and three children older than three years), the macroscopic appearance was considered normal in 20. In the remaining two patients, the noted abnormalities were non-specific.

In 80.6% of patients, no macroscopic or histological pathology was found. The most common histological finding was mild to moderate esophagitis (n=57, 8.9%), and none had severe esophagitis. Of infants with histological evaluation, 95/104 (91.3%) had normal findings. The only findings considered to be significant were two cases of combined severe gastritis and duodenitis/enterocolitis in infants. Of toddlers with histological evaluation, 192/229 (83.8%) had normal findings. Twenty-four toddlers had histological esophagitis, of which 19 were mild and five were moderate. Also, there was one case with eosinophilic esophagitis and another with gastric metaplasia. The histological findings slightly increased among children older than three, however, 251/311 patients (80.7%) had normal findings. Thirty-three children had

histological esophagitis, of which 27 were mild, and six were moderate. The most significant histological findings in this age group were one case with candida esophagitis, one with eosinophilic esophagitis, and one with eosinophilic enteritis. Altogether 148 patients presented with faltering growth and 142/148 (95.9%) had biopsies taken; 27/142 (19.1%) had abnormal findings. In children with normal growth, biopsies were taken in 478/493 (96.7%); 74/478 (15.5%) had an abnormal finding. No significant difference emerged in the number of positive EGD findings between children with normal and poor growth (p=0.36). Table 8 presents abnormal EGD findings concerning the most common EGD indications.

Table 8 Abnormal EGD findings concerning the most common EGD indications in 666 children younger than seven years presenting with non-specific, non-acute symptoms.

Indication	Number (n) of patients with abnormal macroscopic findings (%)	Number (n) of patients with abnormal histological findings (%)
Suspicion of GERD n=268	n= 11/268 (4)	n=44/264 (17)
Common respiratory symptoms n=120	n=1/120 (1)	n=8/115 (7)
Suspicion of IBD n=107	n=6/107 (6)	n=27/107 (25)
Hematochezia (non-IBD) n=50	n= 2/50 (4)	n= 11/47 (23)
Exclusion of anatomic abnormality n=33	n=2/33 (6)	n=1/24 (4)
Dysphagia n= 16	n=2/16 (13)	n=1/16 (6)
Failure to thrive n= 15	n=0	n=1/14 (7)

EGD=esophagogastroduodenoscopy; EoE=eosinophilic esophagitis; GERD=gastro-oesophageal reflux disease; IBD=inflammatory bowel disease

Adverse reactions

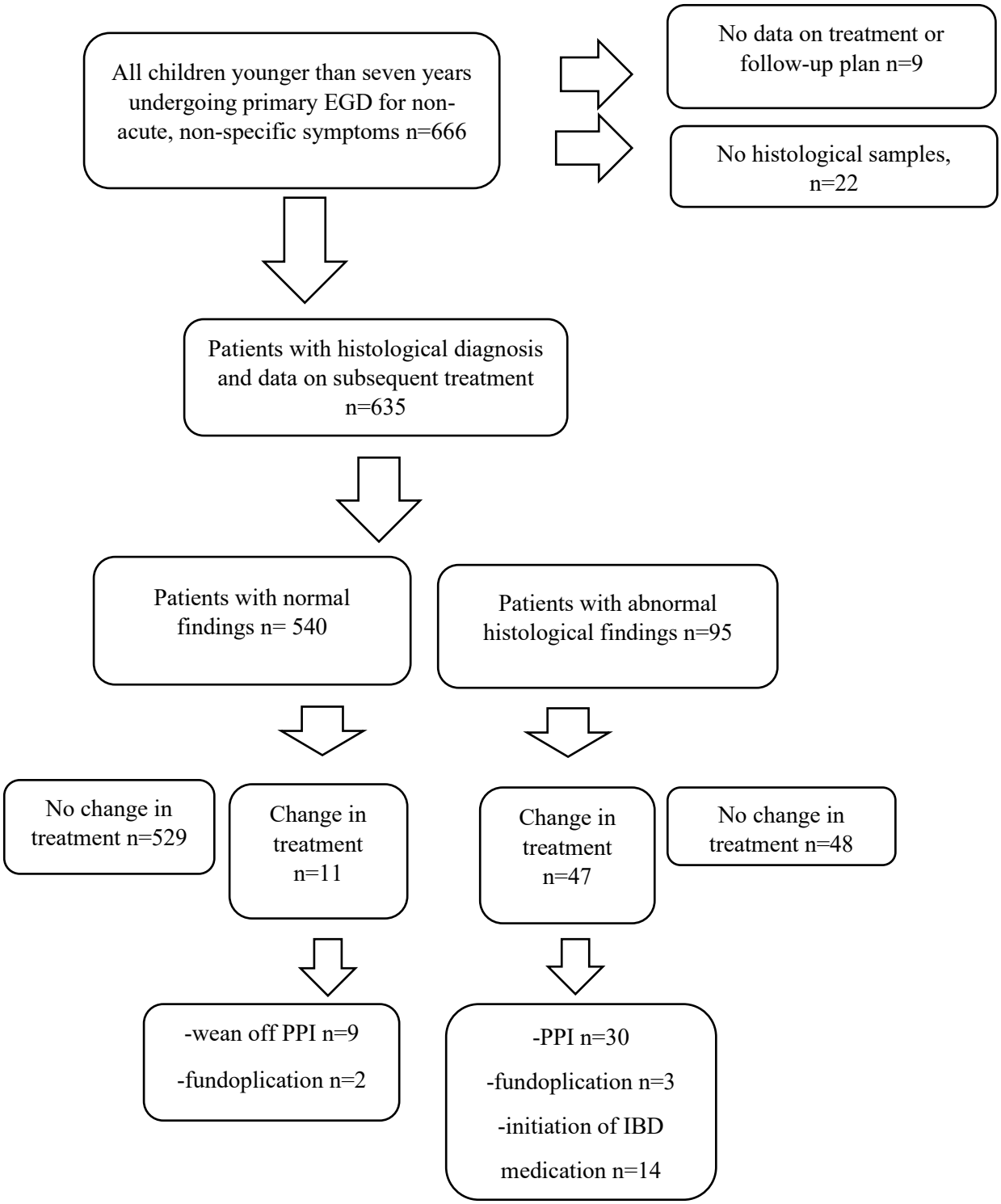
The endoscopy-related adverse effects recorded up to 72 hours after the EGD were minor. Only one patient with a known predisposition to airway obstruction required prolonged hospitalization because of airway problems following extubation. Also, there were three cases of postoperative fever and two cases of wheezing and urticaria.

Role of primary EGD findings in subsequent patient care

Data on subsequent care were available for 657/666 patients (98.6%); for 64/657 patients (9.7%) the results changed the treatment or the follow-up plan. Of these 64 patients, 43 were newly diagnosed cases of IBD. However, among these, EGD findings did not require treatment. If PPI medication was prescribed after an entirely normal EGD, it was not considered an EGD-related change in treatment (n=24). There were no

comments on the patient charts indicating that a negative EGD had benefited the patient or re-assured the parents. The median length of clinical follow-up after the primary EGD at the HUS Children's Hospital was two years (IQR 0.5-5), and only 16/666 patients (2.4%) had no follow-up data on patient charts. During the follow-up period, patients' diagnoses remained unchanged in all but one case where moderate GER-related esophagitis was later recognized as EoE. The impact of the histological EGD results on subsequent care is shown in Figure 2.

Figure 2 Subsequent care after primary esophagogastroduodenoscopy (EGD) in children younger than seven years with non-acute, non-specific symptoms. Data are shown concerning the histological findings. No one had erosive esophagitis. The macroscopic appearance was considered normal in 94% and the changes noted were deemed non-specific.



IBD=inflammatory bowel disease; PPI=proton-pump inhibitor

Role of primary and repeat upper endoscopy in suspicion of GERD (II)

Altogether 268 children had presented with symptoms suggestive of GERD. In Study II, seven patients were excluded because of age older than 18 years and two patients because they had died due to long-term illness before the year 2016. Five patients had not allowed the Patient Data Repository use, and these patients (three males, age range 0.2-12.3 years) were also excluded. Thus, data on 254 children were included, and EGD findings were evaluated in relation to known predisposing conditions for GERD.

The detailed patient selection is described in Figure 1 of Study II. Data presented here also include patients with abnormal findings in the primary EGD. Patient demographics within age groups at the time of primary EGD are shown in Table 9.

Table 9 Patient demographics at the time of primary esophagogastroduodenoscopy in 254 children with symptoms suggestive of gastroesophageal reflux disease (GERD).

	Age <1year n=41	Age 1-2.9 years n=93	Age 3-6.9 years n=120
Gender male/all n (%)	15/41 (37)	60/93 (65)	65/120 (54)
Premature birth n (%)			
<28 weeks	3/40 (8)	2/87 (2)	2/73 (3)
28-32 weeks	2/40 (5)	6/87 (7)	2/73 (3)
33-36 weeks	7/40 (18)	14/87 (16)	10/73 (14)
Predisposing condition to GERD n (%)	9/41 (22)	12/93 (13)	24/120(20)
-Bronchopulmomary dysplasia	n=3	n=0	n=0
-Cerebral palsy	n=0	n=2	n=3
-Congenital syndrome	n=6	n=10	n=18
-Obesity	n=0	n=0	n=3
Abnormal growth n (%)	21/41 (50)	23/93 (24)	25/119 (21)
Eating problem n (%)	26/41 (63)	41/93 (44)	28/118 (24)
Other pre-diagnosed conditions n (%)			
-Asthma	n=1 (3)	n=10 (10)	n=16 (14)
-Constipation	n=5 (12)	n=17 (18)	n=19 (16)
-Non-IgE CMPA	n=1 (2)	n=15 (16)	n=9 (7)
-IgE-mediated allergies	n=0	n=9 (9)	n=3 (3)
No pre-diagnosed condition n (%)	n=18 (44)	n=32 (34)	n=52 (43)

Non-IgE CMPA= Cow's milk protein allergy that is not mediated by immunoglobulin E (IgE) and presents with gastrointestinal symptoms

Problems with feeding or eating were parentally reported for 95/254 children (37.4%). Of children eating poorly, 49% were also growing poorly. More than one-third of the patients had undergone 24-hour pH-monitoring before or at the time of EGD. However, patients who tested positive for acid reflux (acid exposure time >6%)[194] did not have significant difference in the number of histological findings compared with patients testing negative (p=0.59) or receiving no monitoring (p=0.89). Only a few had undergone MII-pH, and thus, no statistical calculations were possible.

The primary EGD had been fully normal in 210/254 patients (82.7%). None had erosive esophagitis. Data on leading symptoms, diagnostic measures, medication, and EGD findings at the time of the primary EGD are shown in Table 10.

Table 10 Data on leading symptoms, diagnostic measures, anti-acid medication, and primary esophagogastroduodenoscopy (EGD) findings in 254 children who underwent the EGD due to symptoms perceived as gastroesophageal reflux (GER).

	Age <1 y n=41	Age 1-2.99 y n=93	Age 3-6.99 y n=120
Symptom leading to the primary EGD n (%) -vomiting -respiratory / silent reflux -non-specific symptoms -heartburn	 n=29/41 (71) n=11/41 (27) n=2/41 (3) n=0	 n=60/93 (65) n=14/93 (15) n=17/93 (18) n=2/93 (2)	 n=53/120 (44) n=18/120 (15) n=13/120 (14) n=28/120 (23)
Duration of symptoms (median, months)	3	12	18
24-hour pH-monitoring n (%)	n=17/41 (41)	n=38/93 (41)	n=44/120 (37)
Positive for acid reflux 24-hour pH-monitoring n (%)	9/17 (53)	22/38 (58)	12/44 (27)
Anti-acid medication at the time of the EGD n (%)	8/41 (20)	15/93 (16)	14/120 (12)
Macroscopic abnormality n (%)	n=1/41 (2) hiatus hernia	n=3/93 (3) non-specific mucosal changes	n=5/120 (4) non-specific mucosal changes (n=4) and yeast like appearance (n=1)
Histological findings n (%)	Mild esophagitis n= 2/41 (5) Moderate esophagitis n= 1/41 (2)	Mild esophagitis n= 13/93 (14) Moderate esophagitis n= 2/93 (2) Gastric metaplasia n=1/93 (1)	Mild esophagitis n= 17/120 (14) Moderate esophagitis n= 6/120 (5) Eosinophilic esophagitis n=1/120 (<1)
Symptoms in patients with histological findings n (%) -vomiting -respiratory / silent reflux -non-specific symptoms -heartburn -abdominal pain	 n=2/3 (67) n=1/3 (33) n=0 n=0 n=0	 n=11/16 (69) n= 3/16 (19) n=2/16 (12) n=0 n=0	 n=12/24 (50) n=2/24 (8) n=4/24 (17) n=4/24 (17) n=2/24 (8)

Five out of nine cases (55.6%) of moderate histological esophagitis were found in patients with known predisposing factors for GER. Among the 31 children who had undergone more than one EGD, the histological grade of the findings remained the same or became less severe, and no one developed

premalignant changes. Table 11 shows the symptoms and EGD results according to the predisposing conditions for GER.

Table 11 Primary esophagogastroduodenoscopy (EGD) findings in 254 children with symptoms suggestive of gastroesophageal reflux disase (GERD). Data are shown in groups with and without predisposing conditions for GERD.

	Patients **without** predisposing conditions to GERD	Patients **with** predisposing conditions to GERD
Number n (%)	197/254 (78)	57/254 (22)
Gender, male n (%)	110/197 (56)	31/57 (54)
Median age at the primary EGD	2.7 y (IQR 1.3-4.5)	2.6 y (IQR 1.0-4.2)
The leading symptom at the primary EGD n (%) -vomiting -respiratory / silent reflux -heartburn -dysphagia -abdominal pain -non-specific	 n= 104/197 (53) n= 35/197 (18) n= 25/197 (13) n= 8/197 (4) n= 7/197 (4) n= 18/197 (9)	 n= 38/57 (67) n= 4/57 (7) n= 5/57 (9) n= 2/57 (4) n=2/57 (4) n= 2/57 (4)
Macroscopic findings at the primary EGD n (%)	n= 7/197 (4)	n=3/57 (5)
Histological findings at the primary EGD n (%)	n=31/197 (16) Mild esophagitis n=24/31 (77) Moderate esophagitis n=4/31 (13) Gastric metaplasia n=1/31 (3) Eosinophilic esophagitis n=2/31 (7)	n=12/57 (21) Mild esophagitis n= 7/12 (58) Moderate sophagitis n= 5/12 (42)

The subsequent care was seldom affected by the primary EGD results. Figures 3a and 3b illustrate subsequent care in patients with normal findings (Figure 3a) and abnormal findings (Figure 3b) in the primary EGD.

Figure 3a Data on subsequent care on 210/254 children with suspicion of gastroesophageal reflux disease and normal findings in primary esophagogastroduodenoscopy (EGD).

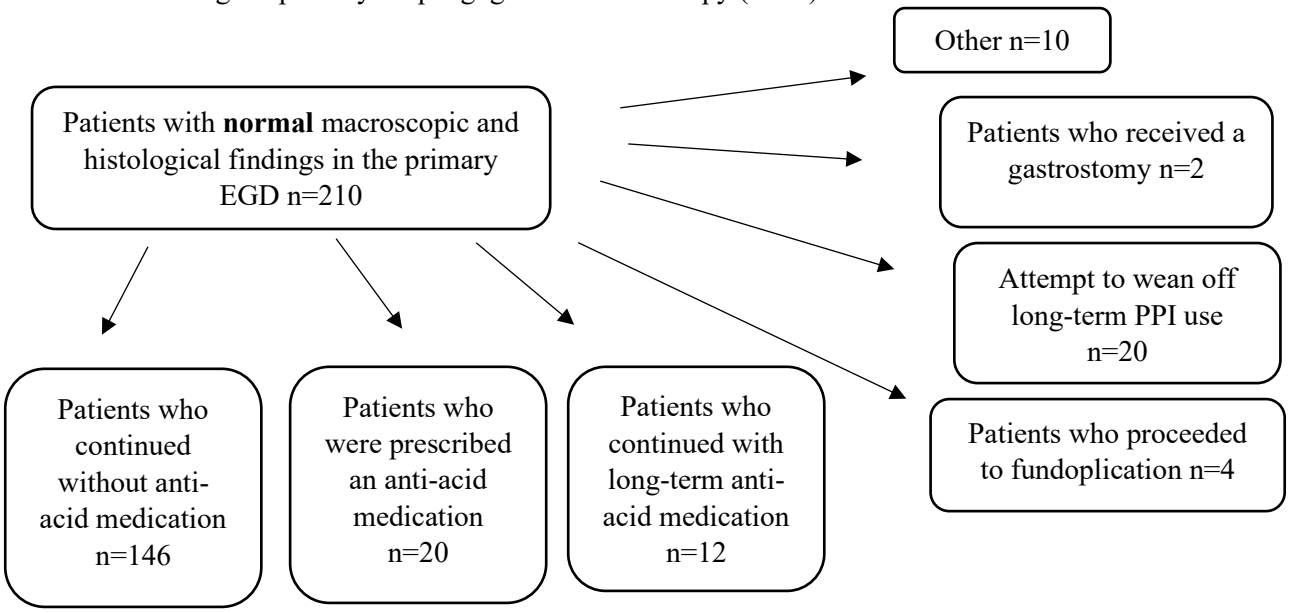
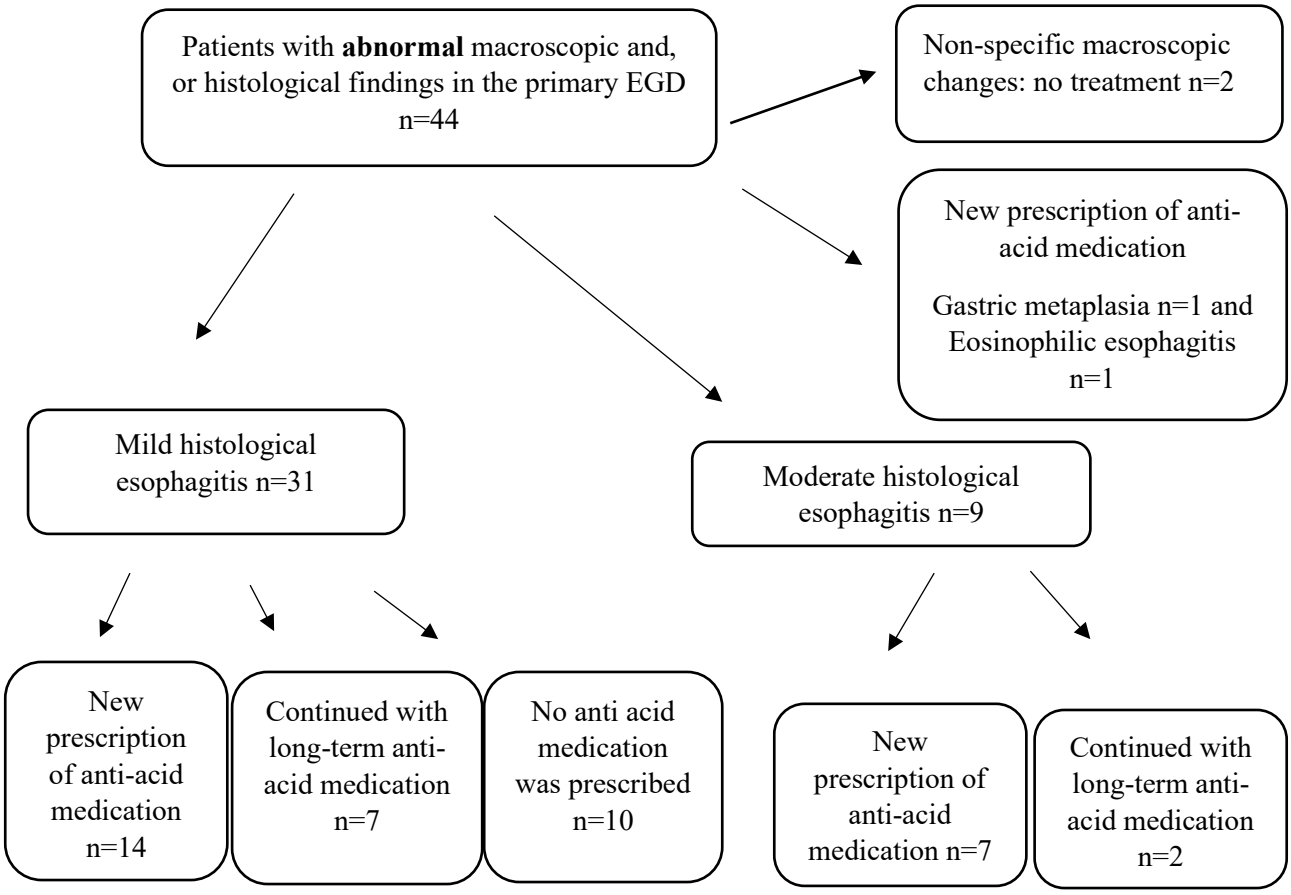


Figure 3b Data on subsequent care on 44/254 children with suspicion of gastroesophageal reflux disease and abnormal findings in primary esophagogastroduodenoscopy (EGD).



Follow-up of children with early childhood GER-related symptoms and normal findings in primary EGD (II)

Of the initial cohort of 210 patients with normal primary EGD findings, access to the Patient Data Repository was denied by 11 patients. Thus, the cohort comprised 199 children both with and without predisposing conditions for GER (n=41 and n=135, respectively) as well as 23 children in whom the initial symptoms at time of primary EGD had been solely respiratory. The median follow-up from the primary EGD for this subcohort was 7.9 years.

Of the 199 study patients, 175 had stated that Finnish is their native language, and they were invited to complete the electronic survey on current GI symptoms, anti-acid medication use, and GI health-related QoL. The main outcomes are presented in Table 12. In addition, 57% of parents reported EGD as not at all useful or only somewhat useful for their child.

Table 12 Data on follow-up outcomes on 199 children who, in early childhood, had undergone an esophagogastroduodenoscopy (EGD) with normal results for symptoms perceived as gastroesophageal reflux (GER).

	Children with initial GI symptoms, no predisposing conditions for GER n=135	Children with initial respiratory symptoms suspected to be related to GER n=23	Children with initial GI symptoms and with a known predisposing condition for GER n=41
Age at follow-up median (IQR)	10.7 y (8.1-13.5)	11.8y (IQR 8.1-13.7)	9.6y (IQR 8.2-13)
Follow-up time median (IQR)	8.1y (IQR 5.2-10.1)	7.9y (IQR 5.2-10.9)	7.6y (IQR 8.2-13)
Number of children with GER-related contacts in patient charts n (%)	n=1/135 (3)	n=0	n=7/41 (17)
Using acid blocker at follow-up based on data from the Prescription Database n (%)	Continuos n=2/135 (2) Occasional n=4/135 (3)	Continuos n=0 Occasional n=1/23 (4)	Continuos n=5/41 (12) Occasional n=4/41 (10)
Number of families who participated in the follow-up survey on current GER symptoms[a] n (%)	n=38/119 (32)	n=6/18 (33)	n=7/38 (18)
Number of children with parentally reported GER symptoms at follow-up n (%)	n=17/38 (45) -daily symptoms n=0 -weekly symptoms n=10 -less often n=7	n=2/6 (33) -daily symptoms n=0 -weekly symptoms n=0 -less often n=2	n=5/7 (71) -daily symptoms n=2 -weekly symptoms n=0 -less often n=3
Number of parents and children who returned the PedsQL GI Module questionnaire[b]	Parents n=31 Children 8-12y n=11 Teenagers 13-17y n=8	Parents n=6 Children 8-12y n=1 Teenagers 13-17y n=1	Parents n=5 Children 8-12y n=2 Teenagers 13-17y n=1

[a]Only patients who speak Finnish as their native language(n=175) were invited to the follow-up survey

[b]Only part of the follow-up participants returned both symptom- and QoL-questionnaires

Follow-up of children with suspected GI-CMPA in infancy (III)

Contact was achieved with 52/57 parents (91.2%) from the original cohort. Of these, 42 mothers agreed to participate in the current follow-up survey. At the time of the DBPCFC, all children (n=57, median age 9 months) had had GI symptoms, such as colicky crying (n=41), vomiting (n=27), constipation (n=12), or diarrhea (n = 32), but no one had FPIES symptoms. At the time of the follow-up survey, the median age of participating children (n=42, 45% boys) was 6.7 (IQR 5.7-8.6) years. The follow-up time was a median of 6 years. According to the result of the DBPCFC the children were divided into DBPCFC-positive (n=12) and DBPCFC-negative (n=30) groups. Patient characteristics are shown in Table 13.

Table 13
Characteristics of children participating in follow-up survey
on early childhood gastrointestinally manifesting cow's milk protein allergy (GI-CMPA) symptoms.
Data are reported as medians and interquartile ranges (IQR) unless otherwise specified.

	All n=42	DBPCFC-positive n=12	DBPCFC-negative n=30
Age at follow-up median (IQR)	6.8y (5.8-8.6)	6.7y (5.8-8.6)	6.8y (5.8-8.1)
Age at the time of the initial DBPCFC (IQR)	0.8y (0.2-3.4)	0.5y (0.2-3.4)	0.8y (0.2-2.1)
Follow-up time (IQR)	5.8y (5.3-6.3)	5.8y (5.4-6.3)	5.8y (5.3-6.1)
Gender male/all (%)	19/42 (45)	6/12 (50)	13/30 (43)
Current GI-symptoms* n (%)	21/42 (50)	7/12 (58)	14/30 (47)
-abdominal pain	14/42 (33)	6/12 (50)	8/30 (27)
-constipation	8/42 (19)	0	8/30 (27)
-diarrhea	5/42 (12)	3/12 (25)	2/30 (7)

*GI symptoms during the last three months at the time of the follow-up survey

All children participating in the follow-up study consumed cow's milk in some form. The QoL measured using the PedsQL Generic Score was good. According to the parental report, no child had been diagnosed with other GI-related diseases, although two DBPCFC-negative children with prolonged non-specific symptoms had undergone an EGD with entirely normal results.

6 Discussion

This thesis reports the school-age outcomes of early childhood common symptoms suggestive of GERD and GI-CMPA, focusing on the role of EGD in the primary diagnosis of non-specific, non-acute GI symptoms in children younger than seven years. Study I revealed that EGD has a limited role in the diagnostic process of non-specific, non-acute GI or respiratory symptoms in infants and young children. The number of positive endoscopic findings was low, and the rare positive findings were mostly found in patients with a clear clinical indication such as suspicion of IBD or regurgitation of known predisposing conditions for GER. No one was diagnosed with erosive esophagitis in the primary EGD. Abnormal growth did not indicate positive EGD findings. The EGD had an impact on the patients' subsequent care in fewer than 10% of patients. Study II further defined the initial diagnostic process, EGD findings, and outcomes of patients presenting with symptoms suggestive of GERD in early childhood. Symptom severity, quality, or 24-hour pH-monitoring positive for acid reflux did not predict positive EGD findings. Study II reported for the first time on follow-up outcomes of early childhood GER symptoms severe enough to require invasive investigations but with entirely normal results in the primary EGD. Follow-up data from registries showed that most of the children had grown out of the GER symptoms, but 3.5% used long-term PPI medication after a median of 7.9 years from the primary EGD. Study III yielded novel data on follow-up outcomes of children with previous symptoms suggestive of GI-CMPA and positive and negative DBPCFC results. The children consumed a regular diet, but many were reported to have current GI symptoms. The few who had also undergone an EGD had had normal results.

6.1 Clinical aspects of diagnostic measurements in young children with non-specific, non-acute GI symptoms

The lack of an objective, gold-standard diagnostic tool for most non-specific GI complaints renders clinical decision-making challenging. An additional challenge in infants and young children is their limited ability to communicate their symptoms. The parents often estimate the burden of symptoms, and this may be influenced by several factors independent of the child's condition.[364]

The number of primary EGDs due to non-specific, non-acute symptoms rose throughout the study period (I). Previously, international guidelines, such as the Rome III criteria for FGIDs, have stated that somatic etiology must be ruled out with sufficient measures.[365] This may have been interpreted as encouragement for invasive investigations such as EGD. The Rome-criteria were revised in 2016, and the Rome IV criteria provide the clinician with a much better tool to approach various GI symptoms. In the new criteria, the previous statement of sufficient diagnostic measures to rule out organic disease was abandoned,[1,13] and clinicians are encouraged to diagnose non-specific, non-acute symptoms with history and clinical examination. The ESPGHAN consensus statement for pediatric endoscopy from 2017 offers weak recommendations with low-quality evidence for EGD in various clinical settings.[356] As the consensus group acknowledges, data supporting the use of EGD in young children are limited.

Here, positive EGD findings were uncommon (I, II). There were only a handful of macroscopic abnormalities among more than 660 patients, and most of these findings were non-specific. No one was diagnosed with erosive esophagitis. The most common suspected disease was GERD, but as has been shown earlier, symptoms do not predict positive EGD findings in children with suspicion of GERD.[23] Most pediatric EGDs have resulted in negative findings,[40,42] and Studies I and II have added to this knowledge pool. There is no evidence that a negative EGD would be beneficial to the patient. On the contrary, Bonilla *et al.* have shown that in children with recurrent abdominal pain, a negative EGD did not decrease symptom burden.[360]

In this cohort of children with GER symptoms, 24-hour pH-monitoring positive for acid reflux did not predict abnormal EGD findings in children with symptoms suggestive of GERD. This is in line with previous research.[201] However, since symptoms do not differ in children with erosive and non-erosive reflux disease,[23] MII-pH monitoring is a valuable tool to distinguish between different reflux phenotypes. In fact, Mahoney *et al.* reported that using MII-pH in diagnosis revealed functional dyspepsia to be the most common phenotype of reflux-related symptoms in children.[207] However, the normative values for pediatric MII-pH have only recently been published.[199] Also, as an invasive investigation, MII-pH should be reserved for patients in whom there are difficulties in diagnosing or treating reflux-related symptoms. Here, only a few patients had undergone an MII-pH study, and the data could not be used.

6.2 Diagnostic yield of EGD in patients in different clinical settings

Study I addresses a cohort of patients commonly seen in pediatric gastroenterological clinics and provides data on their EGD findings and their impact on patient's subsequent care. The diagnostic yield was determined as positive if the EGD results led to a change in patients' subsequent treatment or follow-up plan. Here, the diagnostic yield of the primary EGD was low in the cohort of children with a median age of 2.6 years, as macroscopic findings were rare, and most of the histological findings e.g. mild histological esophagitis were non-specific. Also, in only 10% of the children did the primary EGD results yield information that changed the subsequent care or follow-up plan (I). Most of these patients were diagnosed with IBD, and the EGD findings did not further refine their diagnosis. The impact of EGD in children with suspicion of GERD was similarly low (II). None of our cohort had erosive esophagitis, and the few reported macroscopic abnormalities were accompanied by marked clinical signs of disease such as severe dysphagia leading to weight loss.

Previously, the diagnostic yield of EGD in a pediatric population has been covered in a few studies. Most of these studies report on cohorts significantly older than patients in Studies I and II. Sheiko *et al.* conducted a retrospective cohort study similar to Study I. The most significant difference was that they included all patient groups (aged 1 month to 19 years), whereas Study I contained only children without congenital malformations of the GI or respiratory tract presenting with non-acute, non-specific symptoms. Also, patients with positive celiac serology were excluded from Study I. Sheiko and co-authors reported the diagnostic yield in children younger than 12 years as modest.[319] Study I results are consistent with this as EGD findings were scarce, especially in infants younger than 1 year of age. In contrast, Volonaki *et al*. have reported a large overall percentage of positive endoscopy findings (63%) in their cohort of children younger than one year.[322] However, they provided both upper and lower endoscopy results, and, in the group presenting with non-specific reflux-related symptoms, the diagnostic yield of EGD was much less than what they reported on average. Their patient selection was for the period 1987-2007, and those results may not be comparable with EGD results from 10-15 years later. During that period, the most common indication for EGD was related to upper GI bleeding,[41] and it is likely that the patient material is thus different and not comparable with more recent cohorts.

Also, since the clinical diagnosis of troublesome symptoms and complications is difficult, the latest ESPGHAN GER/GERD guideline from 2018 takes a cautious approach and recommends against the use of EGD as a primary diagnostic tool, using it instead to rule out other etiologies such as EoE, and failure to thrive.[21] In Study I, unsuspected EoE was not found, and altogether for the period 2006-2016, only two patients aged under seven years were diagnosed with EoE, both with substantial dysphagia symptoms and marked allergy background. Although children with EoE are reported to present with such symptoms as vomiting, heartburn, and abdominal pain,[278] there were no difficulties in the differential diagnosis (II).

In children who were reported to grow poorly, the number of clinically significant histological findings did not significantly differ from the corresponding number in children growing normally (I). The results of Study I suggest that faltering growth alone or combined with reflux-related symptoms does not predict positive findings in EGD in young children. Failure to thrive has also been linked to chronic FPIES, a severe form of food allergy in the GI tract [366]. Here, however, no one with a previous suspicion of GI-CMPA had symptoms suggestive of FPIES or vice versa; among patients who underwent the EGD because of failure to thrive, no-one was suspected of suffering from FPIES (I). Of the cohort in Study III, no one of the DBPCFC-positive children had undergone an EGD, but two DBPCFC-negative children whose symptoms were deemed non-specific after the food challenge had undergone a later EGD with entirely normal results.

A substantial proportion (37%) of patients who underwent an EGD for GERD suspicion had parentally reported feeding difficulties. However, no organic cause for the difficulties was identified in the EGD (II). Although the cause of these difficulties was not directly investigated in this study, individual characteristics such as sensitivity to oral sensations or oral motoric skills, and challenges in the parent-child interaction may affect feeding.[367–369]

The clinical suspicion of IBD in this cohort was supported by obvious hematochezia, abnormal laboratory tests, including markedly increased fecal calprotectin. However, the EGD findings were modest, mostly gastritis, and did not require specific treatment.

6.3 Follow-up outcomes of patients with earlier investigations for suspicion of GERD or GI-CMPA

Symptoms attributed to both GERD and GI-CMPA are non-specific, and in both conditions, reaching an objective diagnosis is challenging. In most children without findings in the primary EGD, earlier reflux-related symptoms had dissipated, but 3.5% were using long-term PPI medication. Most of the children currently using PPI medication had a predisposing condition for GERD such as cerebral palsy (II). Empiric anti-acid medication trials have been used to alleviate reflux-related symptoms, especially in older children. The ESPGHAN GER/GERD guideline suggests a PPI trial for 4-8 weeks for children (not infants) with typical GERD symptoms.[21] Long-term PPI use has been associated with potentially harmful alteration of the gut microbiome,[68] increased risk of IBD,[240] and bacterial infections in the GI tract.[370] Among children who had undergone an EGD for symptoms suggestive of GERD in early childhood, current long-term PPI use was uncommon (II).

All children with previous suspicion of GI-CMPA consumed cow's milk in some form. However, many parents of both DBPCFC-positive and DBPCFC-negative children reported current GI complaints in their children (58% and 47%, respectively). This is far more than the 20% of children and adolescents in the general population who are estimated to suffer from at least one FGID.[2] Moreover, 7.6% of children undergoing a primary EGD had a food challenge-proven diagnosis of GI-CMPA (I). This is more than 10-fold the estimated prevalence of 0.6% in food challenge-proven non-IgE CMPA [296] Both IgE- and non-

IgE- mediated cow's milk allergy in infancy have been associated with pain-related FGIDs later in childhood [110].

For both children with prior suspicion of GERD and children with prior suspicion of GI-CMPA, the current GI symptom-related QoL was good (II, III). However, a larger number of participants in the follow-up survey on current reflux symptoms and GI health-related QoL would have been valuable.

6.4 Suggestions for more stringent and evidence-based patient selection for EGD

The number of EGDs that do not contribute to patients' subsequent care is too high (I). Although complications and adverse reactions were uncommon, EGD is an invasive procedure, and its use in pediatric patients should be considered carefully. Previous research has shown an association between exposure to inhaled anesthesia in children younger than two years and learning disorders.[353,371] This finding has been supported by numerous animal models showing neurodegeneration, or neuronal apoptosis, occurs after exposure to inhaled anesthetics.[319] These findings emphasize thorough consideration in patient selection for invasive investigations requiring anesthesia. There has not yet been public discussion on the cost-effectiveness of pediatric EGDs in Finland, but in the US the discussion has been active for some years.[6,42] Without convenient, objective diagnostic tools, reaching a diagnosis for non-specific symptoms is troublesome for the physician and some physicians may even believe the parents want invasive investigations to rule out organic disease. In Study II, however, more than half of the parents who evaluated the primary EGD's usefulness reported it as not at all useful or only somewhat useful for their child.

To ensure proper patient selection for EGD, it is important to educate clinicians to diagnose FGIDs using the clinical Rome IV criteria. As Mahoney *et al.* have shown, the most common GERD phenotype in children is functional dyspepsia, where symptoms are not associated with any reflux events in MII-pH.[207] Also, as EGD findings in young children with non-specific, non-acute symptoms are rare (I, II), the indications for EGD should be evaluated using criteria founded on evidence-based guidelines. When using the guideline criteria, the diagnostic yield of EGD has been shown to be improved.[43]

6.5 Study strengths and limitations

Strengths of this study include the large number of patients from a single center. Nearly all patients had biopsies taken during the EGDs, and there were only a handful of operators and pediatric pathologists interpreting the findings, which adds to the uniformity of the data. The follow-up data from the Patient Data Repository and the Prescription Service, including data on medication purchases, are unique and reliable. The QoL questionnaires applied were validated and well-documented. The GI-CMPA follow-up study's response rate was good, but the sample size was small, and we lost some children to follow-up. Unfortunately, a similar proportion of responders in the follow-up survey of children with prior suspicion of GERD was not achieved. This creates limitations, particularly for the GI health-related QoL results. However, based on the Patient Data Repository, GI symptoms were not reported in the routine school check-

ups. Further, limitations include the study's retrospective design, the medical charts not always being complete, and the lack of healthy control groups in the QoL studies.

7 Summary and conclusion

The long-term outcomes of early childhood non-specific GI symptoms are good. Based on this study, the average prognosis of early childhood non-specific symptoms is excellent. The diagnostic role of EGD is limited in young children without congenital malformations of the GI or respiratory tract who, present with non-specific, non-acute symptoms. Nearly all EGDs in this cohort of 666 children yielded normal macroscopic findings, and the few abnormalities noted were non-specific and minor. No one was diagnosed with erosive esophagitis. The impact of the primary EGD results on the patient's subsequent treatment was modest. In fewer than one in ten children did the results change the treatment or follow-up plan. Especially in infants and in patients with respiratory symptoms as an indication for EGD, positive findings were rare. In children with suspicion of GERD, neither symptoms nor 24-hour pH-monitoring positive for acid reflux predicted diagnostic EGD findings. In children with GER-related histological findings who had undergone repeat EGDs, the histological grade was not altered, and none was diagnosed with premalignant histological changes. In the follow-up studies, both children with previous symptoms suggestive of GERD and children with the earlier suspicion of GI-CMPA had a good health-related QoL. Most of the children had grown out of the GER-related symptoms reported in early childhood by school age, and GER-related morbidity was low. All patients with earlier suspicion of GI-CMPA consumed a regular diet. The health-related QoL was reported as good in both children with previous symptoms suggestive of GERD and children with previous symptoms suggestive of GI-CMPA.

It is necessary to educate clinicians on the limited diagnostic possibilities of EGD in young children with non-specific symptoms. The favorable outcome of early childhood GI symptoms should also reassure both parents and health-care professionals.

8 Implications for future research

The total number of primary EGDs performed in children younger than seven years increased in our clinic during the period 2006-2016. Also, the proportion of patients presenting with non-specific symptoms increased during 2011-2016 (I). Future research on the current clinical practice would yield data on how the new Rome IV criteria have been implemented in our clinic and whether the number of primary EGDs in this patient group with non-specific, non-acute symptoms has already started to decrease. In addition, the prevalence of FGIDs fulfilling Rome IV-criteria should be determined.

Analysis of the esophageal microbiome remains a relatively new field of research. Microbiome alterations have been implicated in the pathogenesis of inflammatory and neoplastic conditions in the colon and elsewhere in the GI tract. The epidemiology of various esophageal conditions, including Barrett's esophagus and EoE, point to the microbiome as a potential co-factor in disease pathogenesis [372]. As the esophageal microbiota resembles the oral microbiota, obtaining saliva samples might help gain data on esophageal microbiota characteristics in various stages and under different conditions during childhood.

Research data on QoL related to GI health in children are limited, and the use of various questionnaires makes it challenging to compare results and build evidence. The newly translated Finnish version of the PedsQL GI Symptoms Scales should be taken into clinical practice to gain QoL data related to GI symptoms in different patient groups across pediatrics. As proxy reports differ from self-reports,[373] the goal should be to persuade the child to self-report whenever possible.

Acknowledgments

This study was carried out between 2016 and 2020 at the Children`s Hospital, Helsinki University and Helsinki University Hospital, Finland. I am grateful to all patients and their caregivers who participated in this study and to everyone who contributed to this project. The work has been conducted mostly remotely from the clinic but under the careful supervision of Professor Kaija-Leena Kolho and Docent Laura Merras-Salmio who share a passion for high-quality clinical research. I am grateful to have had the opportunity to learn from both of you. Thank you for your patience; my pace is sometimes a bit frantic. I warmly thank the reviewers of this thesis, Professor Kalle Kurppa and Assistant Professor Marko Kalliomäki for insightful comments that greatly improved the manuscript. My gratitude is also owed to my co-authors Professors Mika Mäkelä and Risto Rintala and Docent Erik Qvist for their contributions. I also thank Docent Taina Arvola and Henrikka Aito, PhD, for serving the thesis follow-up committee. Registered Nurse Anne Nikkonen is also gratefully acknowledged.

Finally, a giant thanks to my family for keeping my feet firmly on the ground. Your love reminds me always of the essential things in life.

I hope that everyone reading this thesis enjoys it and can learn something new from it.

Helsinki December 31, 2020

Noora Helin

This work has been financially supported by the Signe and Ane Gyllenberg foundation, and the Foundation of Pediatric Research. I am most grateful for their support.

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